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YAFFE AWARD LECTURE

Managing Asthma: Past, Present, and Future

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Asthma has been recognized in the medical literature for almost 2000 years. Modern pharmacotherapy for asthma began with the commencement of the 20th century following the development of epinephrine and the demonstration of its effectiveness for acute symptoms of asthma. Progressive development of this class of bronchodilator medication has provided greater β2 specificity and longer duration of action. Corticosteroids were introduced about 50 years ago. As a systemic medication, they provided anti-inflammatory activity that continues to be essential for exacerbations of symptoms that are unresponsive to a bronchodilator. Corticosteroids were subsequently developed as inhaled agents for long-term maintenance therapy. The availability of corticosteroids with high topical effect has permitted the use of smaller doses with minimal systemic effect; therefore, the inhaled corticosteroids have become the most effective monotherapeutic agents for chronic asthma.

Both theophylline and long-acting β2 agonists (e.g., salmeterol) provide additive clinical effect to small doses of inhaled corticosteroids. This effect is greater than that achieved with larger doses of the inhaled steroid used alone. A new approach to managing allergic asthma is now available in the form of a monoclonal antibody directed against immunoglobulin E (IgE). This agent, omalizumab, binds to circulating IgE, thereby preventing IgE from binding to mast cells. This subsequently prevents the release of mediators for bronchospasm and inflammation. Under investigation are monoclonal antibodies to modify the effects of interleukins involved in the inflammatory process of asthma. Phosphodiesterase inhibitors that are more specific than theophylline and monoclonal antibodies that prevent the attachment of rhinovirus to respiratory mucosa are being studied. Since rhinoviruses are major causes of acute exacerbations of asthma, these and other measures to prevent or modify the common cold provide great potential for further improvement in the outcome of asthma.

KEYWORDS: asthma

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ASTHMA: THE DISEASE

"If from running, gymnastic exercises, or any other work the breathing becomes difficult, it is called Asthma. The symptoms are heaviness of the chest, sluggishness to one's accustomed work; they are hoarse and troubled with cough; and if these symptoms increase they sometimes produce suffocation." [Aretaeus (c.A.D.120 180): On the causes and symptoms of chronic diseases]

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"This disorder starts with a common cold, and the patient is forced to gasp for breath day and night, until the phlegm is expelled, the flow completed and the lung well cleared." [Moses Maimonides (A.D. 1135-1204): Treatise on Asthma]

These quotations from the ancient medical literature demonstrate the duration of our awareness for the clinical entity known as asthma. The above descriptions are consistent with a pragmatic definition of asthma arrived at by a committee of the American Thoracic Society in 1962: *"Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."*[1] Berkart first de-

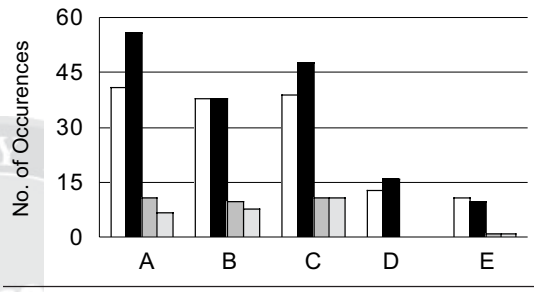
scribed the importance of what we now recognize as the inflammatory component of asthma with the description *"The desquamation of the epithelium is followed by a copious emigration of leukocytes. In contact with the fibrinoplastic substances, which exude at the same time, the white corpuscles disintegrate.""*(Asthma: its pathology and treatment. London: Churchill, 1889).

EVOLUTION OF EFFECTIVE PHARMACOTHERAPY

Modern treatment of asthma can be dated to the observations of Solis-Cohen who described an "adrenal substance" that provided benefit for asthma.[2] Benefit from injected epinephrine was noted in 1903.[3] Ephedrine, an oral agent with epinephrine-like properties, was identified in 1925 as an active ingredient in the Chinese herb, Ma Huang.[4] Further development of this class of drugs led to agents with more specific β2 adrenergic effect and longer duration of action (Table). Although anecdotal descriptions of the benefit from coffee date back to at least the middle of the 19th century, the medical use of the most effective of the xanthines, theophylline, was not documented until 1937.[5] A subsequent publication three years later described the use of oral theophylline in combination with ephedrine.[6] That was followed by the marketing of multiple pharmaceutical preparations containing fixed dose combinations of ephedrine and theophylline; these formulations remained the most common medications used to treat asthma for the next 35 years.

The use of these combination products declined precipitously following controlled clinical trials demonstrating that ephedrine increased adverse effects without adding clinically important benefit.[7,8] Theophylline alone in larger doses than had been used previously was highly effective in controlling symptoms of chronic asthma (Figure 1). These findings led to the use of theophylline as a maintenance preventative medication that was more effective than alternatives proposed for that purpose.[9-11]

Figure 1. Number of symptomatic 8 hour patient observation periods. Twelve children with acute symptoms of asthma received five drug regimens in a randomized double-blind study. Each child received a week-long trial of: placebo (Intervention A); ephedrine and aminophylline in "small" dose combinations that were customary for the time (Intervention B); "large" dose ephedrine (Intervention C); "large" dose theophylline (Intervention D); and""large" dose ephedrine and theophylline (Intervention E). With or without ephedrine, "large" doses of theophylline that maintained serum theophylline concentrations between 10 and 20 μg/mL was highly effective. Conventional doses for the time were not more effective than placebo in these patients. Adverse effects differed from placebo only when ephedrine was added to the theophylline.[7]"



□ = *Symptomatic;* ■ = *Inhaled Bronchodilator;*
▩ = *Injectable Epinephrine;* □= *Substituted Medication*

However, the effective and safe use of theophylline required characterization of both its pharmacodynamics and its pharmacokinetics. The initial studies demonstrated that serum theophylline concentrations of 10–20 μg/mL provided optimal therapeutic benefit.[7,8] These findings were consistent with reports by others.[12] The variable rate of elimination required individualization of dosage to attain those optimal concentrations.[13-16] The rapid rate of absorption and elimination from plain tablets resulted in fluctuations in serum concentration. This variability in theophylline concentrations had the potential to cause unacceptable degrees of therapeutic effect. This led to the development of slow-release theophylline formulations that produced more stable serum concentrations and clinical effect with the advantage of twice daily dosing.[17,18] Serum theophylline concentrations that exceeded 20 μg/mL were associated with progressively increasing risk of toxicity;[19] however,

Table 1. Development of Sympathomimetic Bronchodilator Medications Arranged Generally from the Oldest to the Most Recently Marketed

Parenteral and inhaled	**Oral**
Epinephrine (adrenalin)	Ephedrine
Isoproterenol (isoprenaline)	Metaprotenol (orciprenaline)
Isoetharine	Terbutaline
Metaproterenol (orciprenaline)	Albuterol (salbutamol)
Bitolterol	
Terbutaline	
Pirbuterol	
Albuterol (salbutamol)	
Formoterol	
Salmeterol	

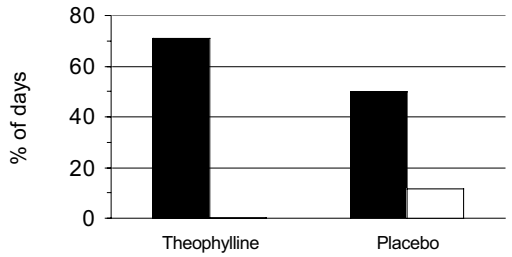
doses that maintained the concentrations within the 10–20 μg / mL reference range were generally devoid of even concerns about behavior and learning effects.[20,21]

Adrenal corticosteroid hormones were demonstrated to be of value for asthma in the 1950s.[22] Although controversies concerning their use have persisted, the value of these agents, given orally or parenterally for acute exacerbations of asthma, is now well established.[23,24] However, doses that were safe and effective for the short-term treatment of exacerbations were not safe for prolonged use. This led to the development of corticosteroids dosage strategies that were safe as maintenance therapy for the management of persistent symptoms. Alternate-morning use of prednisolone, prednisone (the inactive pro-drug of prednisolone), and methylprednisolone were used to control chronic asthma with acceptable safety.[25] Inhaled corticosteroids were introduced in the late 1970s. Inhalation therapy allowed the administration of medication with potent topical effect in sufficiently small enough doses to minimize systemic effects. A small degree of depressed hypothalamic-pituitary-adrenal axis function could be demonstrated for both the inhaled and alternate-morning oral regimen.[25,26] No difference in growth was apparent between these regimens. The inhaled corticosteroid appeared to be effective for those individuals who were not optimally controlled with the alternate-morning oral regimen.

Low doses of inhaled corticosteroids were somewhat more effective than theophylline for controlling chronic asthma.[27,28] Moreover, they were easier to use because they didn't require serum concentration monitoring and had no potential for acute overdose. Nonetheless, theophylline continued to be useful as an additive agent to both alternate-morning prednisolone and inhaled corticosteroids (Figure 2).[29,30] Demonstration that theophylline had anti-inflammatory effects added to the continuing interest in using this medication.[31] Likewise, the long-acting β2-agonist (e.g., salmeterol) has a similar additive effect to that noted with inhaled corticosteroids.[32,33] Salmeterol is not only easy to use, but it is marketed as a combination inhaler with an inhaled corticosteroid. Unfortunately, these long-acting agents may down-regulation of the β2-receptor in a subset of patients. A consequence of down-regulation is the loss of bronchopro-tective effect of shorter-acting β2-agonists when used as rescue medications or to prevent exercise-induced bronchospasm (Figure 3).[34]

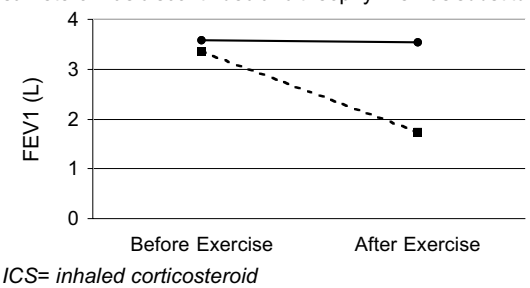
Other moieties with unique mechanisms of action have been introduced. Cromolyn sodium (disodium cromoglycate) and nedocromil pharmacologically act to inhibit the release of mediators from mast cells and basophils. However, their very modest degree of effect and 4-times-daily administration have made them of little clinical interest when compared to alternative therapies. More recently, leukotriene modifiers have been introduced. These medications selectively bind to the cysteinyl leukotriene receptor

Figure 2. Percent of symptom free days and excessive inhaled bronchodilator usage among 21 children receiving theophylline or placebo as additive medication with inhaled corticosteroids. Theophylline added to an inhaled steroid was associated with significantly more symptom-free days and virtually eliminated days when excessive inhaled bronchodilator was used.[29]



■=Symptom-free; □ =Excessive Inhaled Bronchodilator

Figure 3. FEV_1 before and after 6 minutes of treadmill exercise at a speed and incline sufficient to maintain the heart rate at 85% of aerobic capacity in a 15-year-old male with severe chronic asthma and exercise intolerance.[34] The results are the mean of two tests performed on different days while the patient was being treated with salmeterol and high dose inhaled corticosteroids and two tests subsequent to stopping the salmeterol and adding theophylline to the same dose of inhaled corticosteroids. Each exercise test was preceded by 4 inhalations of pirbuterol (a therapeutic equivalent of albuterol) from a Maxair Autohaler. Despite the pre-exercise administration of the pirbuterol, the FEV_1 decreased by 40 and 60% on the two days while receiving salmeterol. Exercise-induced bronchospasm was completely blocked when sameterol was discontinued and theophylline was substituted.



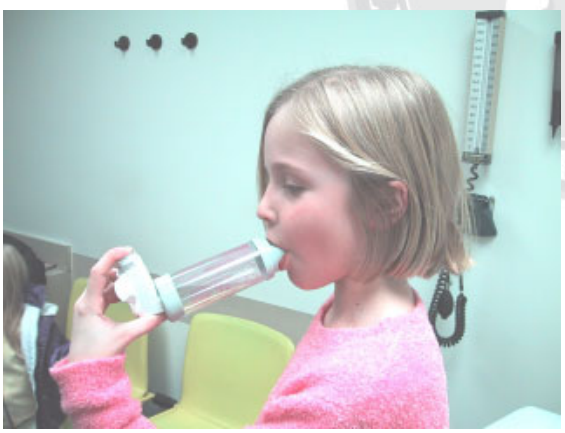
ICS= inhaled corticosteroid
■=ICS + Salmeterol; ●= ICS + Theopylline

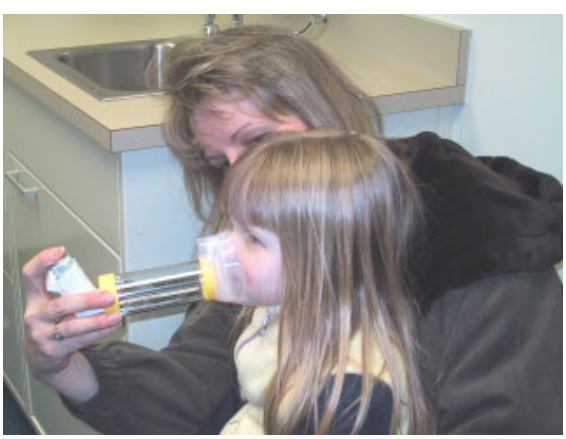
to inhibit the action of leukotrienes released from mast cells. Montelukast has been the leading medication in this class. Controlled clinical trials have shown measurable benefit; however, the effect is generally small.

CURRENT STATE OF THE ART FOR PHARMACOTHERAPY FOR ASTHMA

Currently available therapeutic options have the potential to minimize morbidity and provide normal functioning for most patients. Acute symptoms can generally be relieved by an inhaled β2 agonist administered via a metered dose inhaler (Figure 4). The progression of an acute exacerbation, most of which are triggered by viral respiratory infections, can usually be stopped by the use of a short course of oral corticosteroid.[35,36]

Figure 4. Demonstration of inhaled medication from a metered dose inhaler (MDI) with a valved holding chamber in a pre-school age child (upper photo) and with a face mask in a toddler (lower photo). The MDI injects aerosol into the chamber with one way valves that permits inhalation of the medication from the chamber while exhalation is into the ambient air. Three to six actuations of albuterol (90 mg/acutation) in this manner with at least 3-4 breaths after each actuation to evacuate the chamber provides bronchodilator effectiveness equivalent to 2.5 mg of albuterol by open nebulizer.[61]





A small dose of inhaled corticosteroid is the most effective and safe monotherapeutic regimen for chronic asthma. The use of a combination of low dose inhaled corticosteroid with salmeterol is generally more effective than a larger dose of an inhaled steroid. For this reason, the combination of the two medications is the primary regimen of choice when low doses of inhaled corticosteroid have failed to control the disease. Alternatively, theophylline can be used as an additive agent in the sub-group of individuals who develop salmeterol-induced loss of response to the rescue or bronchoprotective effects of albuterol or pirbuterol.[34] Montelukast may be useful for very mild daily symptoms in young children where delivery of an inhaled medication is problematic.

The most common form of asthma in young children is an intermittent pattern characterized by exacerbations from viral respiratory infections.[37] Highly successful outcomes for this pattern of asthma are attained with intervention measures that include a systemic corticosteroid.[38,39] Parents are given a limited supply of oral corticosteroid and instructions for its use. Because it can be given as soon as the response to bronchodilator therapy is incomplete, this type of self-management permits initiation of more prompt and effective treatment than is likely to occur when a patient must first go to a physician's office or emergency department. The addition of maintenance medication, including inhaled corticosteroids, does not prevent viral-induced exacerbations and is therefore not indicated for this pattern of asthma.[40-42]

Although all healthcare providers have access to the same medications, outcome varies greatly among different practitioners. Asthma-associated hospitalization is a major component of morbidity. Unfortunately, there have been no signs of decreased hospitalization over the past 20 years despite the widespread distribution of the 1991 national guidelines for the management of asthma (Figure 5).[43] This continuing high hospitalization rate reflects the practice in the general medical community. Conversely, specialty programs have consistently had fewer emergency care visits and lower rates of hospitalization.[39,44-46] This reflects more skilled decision

making, closer follow-up with regularly scheduled visits, use of physiological measurements of lung function, and more time and effort spent on patient education.[47]

WHAT'S NEXT?

The newest therapeutic modality with a unique mechanism of action is a monoclonal antibody that is directed against immunoglobulin E (IgE). This agent (omalizumab; Xolair) profoundly decreases the amount of the immunoglobulin class that contains specific antibody to inhalant allergens. It does this by adhering to the high affinity binding sites on the IgE molecule. Allergic respiratory symptoms occur when an IgE antibody, which is bound to the high-affinity receptor [Fc(epsilon)RI] on mast cells, interacts or cross-links with an allergen to cause the release of mediators. It is this IgE antibody high-affinity receptor cross-linking that interacts with an allergen to cause release of mediators that result in allergic respiratory symptoms.

The anti-IgE minimizes the potential for an allergen to cause mediator release by tying up the binding sites on the IgE molecule. Over time, this is associated with down regulation of the high-affinity receptors (Figure 6).[48] The use of this new agent is hampered by the availability of alternative medications, the very high cost of this medication, and its limitation to affect the allergic component of asthma. For these reasons, omalizumab is currently used in highly selective patients who have an identified major allergic component to their disease and whose asthma is poorly controlled with conventional therapy.

Since multiple mediators are involved in the inflammatory component of asthma, the development of new therapeutic modalities has focused on antagonists to those mediators. Interleukin 4 (IL-4) appears to play an important role in the inflammatory component of asthma. Soluble recombinant human IL-4 receptor (IL-4R) inactivates human IL-4 without mediating cellular activation. An inhaled dose of this agent is reported to have pharmacodynamic or pharmacokinetic activity that is characterized by a serum half-life of about one week. Measurable antiasthmatic effect has been reported with the use of this agent.[49,50] A humanized monoclonal antibody directed against IL-4 has also been developed, and studies are planned.[51] Interleukin 5 (IL-5) appears to be essential for the formation

Figure 5. Hospitalization rate from the National Hospital Discharge Survey, National Center for Health Statistics, Center for Disease Control.[43] Pre-school age children with an annual rate of about one hospitalization per 200 children in that age group have twice the hospitalization rate for asthma of children 5–10 years of age and about 5 times the rate for children ages 11–17 years.

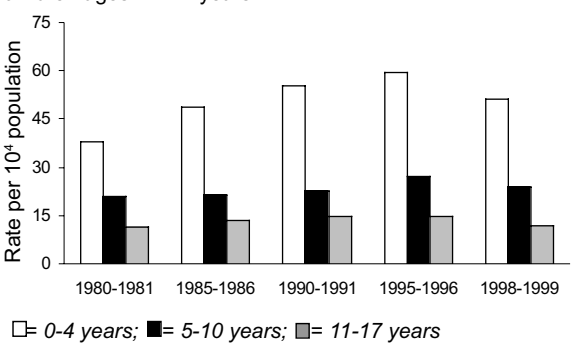
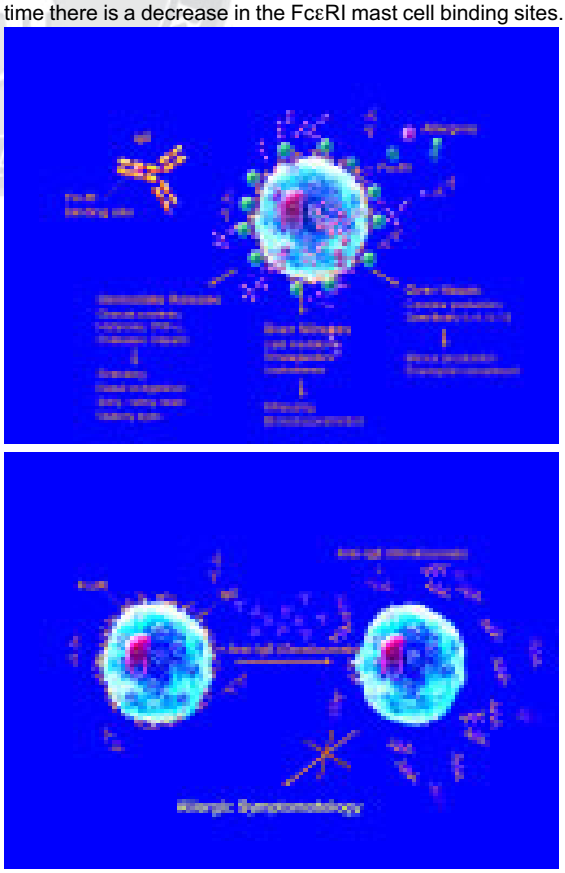


Figure 6. Effect of IgE on release of mediators of asthma from mast cells. The binding site on the IgE molecule binds to the high affinity receptor on the mast cell (Fc,RI). Bridging of the mast cell bound IgE by allergen results in release of the mediators (upper figure). Omalizumab binds to the Fc,RI binding site on the IgE molecule, thereby preventing it from binding to the high affinity receptor on the mast cell. Over time there is a decrease in the FcεRI mast cell binding sites.



of eosinophils, which are thought to have a major role in the pathogenesis of asthma. A single dose of a monoclonal antibody to IL-5 decreases blood and sputum eosinophils for weeks. However, clinical efficacy has yet to be demonstrated.[52,53]

Recognition of the anti-inflammatory effects of theophylline, which is mediated through its effect on phosphodiesterase enzymes, has led to interest in more specific phosphodiesterase inhibitors that are associated with less potential for adverse effects than theophylline.[54-58] While further developments in this class continue, none have yet shown clinical advantage over theophylline.

Viral respiratory infections are a major cause for acute exacerbation of asthma. For this reason, the greatest need for future developments must focus on therapies that effectively deal with viral-associated exacerbations. An effective vaccine for respiratory syncytial virus (RSV) would potentially prevent the most common cause of hospitalization in infants beyond the neonatal period and the most common cause of recurrent asthmatic episodes in pre-school age children.[37] Since the rhinoviruses predominate as a major trigger for acute asthma, among school age children and adults, prevention or effective anti-viral treatment of the common cold could be invaluable in improving asthma control. Since the intercellular adhesion molecule-1 (ICAM-1) is the cell surface receptor for human rhinoviruses, use of recombinant soluble ICAM-1 as a preventative has been under study.[59,60]

CONCLUSIONS

Managing asthma has progressed from the earliest days when treatment was focused on measures that provided short-term relief of symptoms. The introduction of corticosteroids enabled the inflammatory component of asthma to be modified. Pharmacological development of corticosteroids with high topical potency that could be given by inhalation overcame the toxic potential associated with prolonged oral use and largely replaced the role of theophylline as the major maintenance medication for chronic asthma. The addition of salmeterol or theophylline provides greater efficacy than larger doses of inhaled corticosteroids. A monoclonal antibody against IgE provides a new potential treatment for selected patients. For the future, we may see successful application of agents that target specific mediators, but the data will have to be more impressive than has been seen with leukotriene modifiers. Investigations continue to identify more specific phosphodiesterase inhibitors in the hope of obtaining the efficacy and anti-inflammatory effect of theophylline without its narrow therapeutic range and potential for adverse effects. Perhaps the future will eventually provide an effective RSV vaccine and measures that can prevent the other viral respiratory infections that are the major triggers of acute exacerbations of asthma. While we await further advancements, including a cure for the common cold, the morbidity from asthma is already effectively minimized in specialized care programs utilizing the effective and safe medications currently available accompanied by patient education in the appropriate use of those agents.

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REVIEW ARTICLE

Type 2 Diabetes Mellitus in Children and Adolescents: The New Challenge

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The epidemic increase in the incidence of type 2 diabetes mellitus (T2DM) in children and adolescents is presenting enormous challenges to the medical profession. The combination of factors such as obesity, ethnicity, puberty, and genetic predisposition has contributed to the development of T2DM in younger ages. These factors affect the regulatory mechanism of insulin secretion, insulin action, and hepatic gluconeogenesis. In contrast to adults, children appear to have a shorter latency to disease, a more rapid development of symptoms, and an increased ketoacidosis. There are limited therapeutic options to prevent or manage T2DM in children. Although the role of diet and exercise (lifestyle intervention) has not been adequately evaluated in children, they will remain important adjuncts in the prevention and treatment of T2DM. Insulin and metformin are currently the only approved medications for the treatment of T2DM in children. Clinical trials involving other oral agents used in adults are currently being conducted to evaluate their safety and efficacy in children.

KEYWORDS: drug therapy, obesity, pediatrics, type 2 diabetes mellitus

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ABBREVIATIONS: DM, diabetes mellitus; GDM, gestational diabetes mellitus; GIP, glucose insulinotropic peptide; GLP-1, glucagon-like-peptide 1; NEFA, non-esterified fatty acids; PAI-1, plasminogen activator inhibitor-1; T1DM, type 1 diabetes; T2DM, type 2 diabetes mellitus; VLDL, very low-density lipoproteins; ADA, American Diabetes Association; DKA, diabetes ketoacidosis; FDA, Food and Drug Administration; LDL, low-density lipoprotein; HDL, high-density lipoprotein

INTRODUCTION

Diabetes mellitus (DM) is a group of complex metabolic disorders characterized by hyperglycemia due to inadequate insulin secretion, peripheral insulin resistance, and increased hepatic gluconeogenesis. Depending upon which underlying impairment(s) are present, classifications of diabetes have emerged. Type 1 diabetes (T1DM), the most common type of DM in children, is usually mediated by an autoimmune destruction of pancreatic b-cells, resulting in little to no insulin production. Type 2 diabetes mellitus (T2DM), traditionally viewed as an adult disease, is the result of a failure of pancreatic β-cells to secrete adequate amounts of insulin to compensate for the marked insulin resistance and increased hepatic gluconeogenesis.[1] The prevalence of T2DM is now increasing in children and adolescents, particularly in those genetically predisposed, and is paralleling the rise of obesity that is being fueled by sedentary lifestyle and dietary indiscretions.[1-6]

The increasing prevalence of T2DM in this younger population will significantly impact the medical, financial, and health of humans worldwide. A multidisciplinary team of physicians, nurses, nutritionists, pharmacists, and educators must be thoroughly trained to meet the challenges. The improved awareness of health care providers of the growing problem of T2DM in

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children will enhance the identification of at-risk children, improve diagnostic criteria, and improve management. The earlier development of T2DM poses an enormous financial burden to the health care system, leads to a reduction in productivity associated with a chronic disease, and reduces life expectancy. The human element is self-evident in the lives of the children affected and their families, whose daily lives are fraught with profound psychosocial and physical comorbidities.

The goal of this paper is to review of epidemiology, pathophysiology, and complications of T2DM in children and adolescents and to focus on options for prevention and treatment.

EPIDEMIOLOGY

Childhood T2DM is becoming a worldwide epidemic with increasing incidence reported in the United States (U.S.),[3-9] Canada,[10,11] Japan,[2,12,13] and Libya.[14] The rise in the incidence of T2DM has paralleled the increasing rate of childhood obesity.[20] In the U.S., T2DM in children was first reported in a Pima Indian population[15] and now predominates in certain ethnic groups including Asians,[2,12,13] Hispanics,[16,17] American-Indians,[7,15] and African-Americans.[5,18]

Pinhas-Hamiel reported a 4-fold increase in T2DM in the Greater-Cincinnati area, from 2–4% of new DM cases in 1982 to 16% in 1995.[3] The incidence was even higher (33%) for children between 10 and 19 years of age.[3] Among Mexican-American children, Neufeld reported that T2DM among Mexican-American children accounted for 31% of diabetes cases diagnosed between 1990 and 1994.[17] In the Mid-South portion of the US, mainly in African-American children, Scott reported an increased incidence of T2DM from 4% of new cases in 1988 to 34% in 1995.[4,5] Burghen reported a five-fold increase in T2DM in the Greater-Memphis, Tennessee area between 1990 and 2000.[18] The American Diabetes Association has stated that 8- 45% of children newly diagnosed with DM have T2DM.[19]

PATHOPHYSIOLOGY

The pathogenesis of T2DM in children and adolescents is poorly understood. The pathogenic mechanisms involve derangements in blood glucose regulation, impaired insulin secretion, insulin resistance, and increased hepatic gluconeogenesis. Risk factors for the development of T2DM include ethnicity, genetics, obesity, unhealthy lifestyle, gender, and puberty. Studies in minority children demonstrate more risk factors for the development of T2DM than those reported for their Caucasian counterparts. Differences in risk factors among African-American and Caucasian children include an increased β-cell activity, higher insulin secretion, reduced insulin clearance, and lower insulin sensitivity among African-American children.[20-23] African-American children with T2DM are more obese and have a more sedentary lifestyle, have a greater percentage of their caloric intake as fat, have lower resting energy expenditure, and lower rates of lipolysis. It is not clear if these factors associated with hyperinsulinemia are due to race-related intrinsic differences, lifestyle, or other biological factors, but these factors could easily explain the higher prevalence and incidence of children with T2DM in minorities.

T2DM is likely a polygenetic disease resulting from the interaction of multiple genes with environmental factors. The higher prevalence of T2DM in children of minority racial background, a history of macrosomia or underweight at birth, and a family history of DM suggest that genetic factors play an important role in the development of the disease.[2-4,16-18,24] However, many years are required for gene mutations to occur; therefore, the recent dramatic rise in the incidence of T2DM in children cannot be explained by a change in the genetic pool. Lifestyle changes in children with genetic risk predisposition are the most likely cause for the increased incidence of T2DM. The role of increased adiposity in the pathogenesis of T2DM has been demonstrated in the parallelism of both obesity and the T2DM epidemic and in the higher prevalence of T2DM among overweight and obese adolescents.[19,25,26] The severity and the duration of obesity, as well as the distribution of fat, have an important role in the genesis of T2DM.[27-32] Central obesity appears to have a greater influence on insulin sensitivity than peripheral obesity.[28] The relationship of excessive adipose tissue and the development of insulin resistance is not completely understood. Increased levels of non-esterified fatty acids associated with obesity may directly affect β-cell function, insulin secretion, and insulin resistance leading to glucose intolerance.[33-35] High plasma

non-esterified fatty acids concentrations may also impair the release of incretins. Incretins are major regulators of pancreatic insulin secretion that are released by intestinal cells in response to nutrient intake.[36] Two incretins, glucagon-like-peptide 1 (GLP-1) and glucose insulinotropic peptide and glucose-dependent insulinotropic peptide (GIP), are responsible for 80% and 20%, respectively, of the intestinal incretin effect on pancreatic insulin secretion.[37] Decreased GLP-1 and GIP responsiveness in obese subjects may be an important factor in the development of impaired glucose tolerance.[38]

Sedentary lifestyle is an independent risk factor in the pathogenesis of T2DM.[39,40] Lower prevalence of T2DM has been found in subjects with increased levels of physical activity independent of the adiposity (i.e., Sumo wrestlers). Insulin sensitivity positively correlated with the maximum aerobic capacity in adult Pima Indian and Caucasian men with normal glucose tolerance.[24] Hyperinsulinemia has been associated with lower levels of physical activity in children.[41] Increases in physical activity improve insulin action, indices of insulin resistance, and glucose metabolism in both lean and obese subjects with or without T2DM.[42]

Gender is another factor associated with the development of T2DM in children. The male-to-female ratio in adolescents with T2DM has ranged from 1:1.6 to 1:2.8.[3,4,43] These data suggest that females are at greater risk than males for developing T2DM. The underlying cause for the greater prevalence of T2DM in adolescent females is unknown. However, girls gain more weight, have increased fat mass, decreased physical activity, and are more insulin resistant than boys during adolescence.[44]

Puberty is a peak time for the development of T2DM in children. Hormonal changes during puberty and increased secretion of growth hormone and sex hormones, antagonize insulin action, promoting insulin resistance and hyperinsulinism.[45-49] Glucose disposal rates are lower during puberty compared with pre-puberty and post-puberty rates.[46] Caucasian children compensate for the insulin resistance during puberty by secreting more insulin whereas compensation in African-American children may be reduced. These factors in conjunction with an increase in body fat (predominately in females) and a decrease in physical activity may explain the higher incidence of T2DM in African-American females.[43]

Progression from normal glucose tolerance through impaired glucose tolerance to T2DM is affected by a number of complex factors, the degree and order of which has yet to be elucidated. It is imperative that well-designed studies be implemented to improve the understanding of the pathogenesis and natural course of this challenging problem.

CLINICAL PRESENTATION

Children with T2DM are usually obese, from a minority group, and have a family history of diabetes. They may also have dyslipidemias, menstrual irregularities, hypertension, acanthosis nigricans, and microvascular changes.[50] Newly diagnosed children may present with mild to severe clinical symptoms. Approximately one third of these children present with glucosuria and hyperglycemia that may be detected during routine medical exam.[23,27,42,44] About 20–25% of children with T2DM may present with severe symptoms of polydipsia, weight loss, ketonuria, and ketoacidosis.[13,45] Hyperglycemia, ketonuria, and metabolic acidosis are usually milder in children with T2DM than in T1DM patients. Plasma insulin and c-peptide concentrations are usually higher in T2DM than in T1DM, reflecting insulin resistance; however, levels may also be normal or low at the time of diagnosis.[17] Children do not appear to have the long latency period seen in adults; rather, they develop symptomatic polyuria and nocturia early in the disease process.

The American Diabetes Association criteria for the diagnosis of diabetes is a fasting blood glucose ≥126 mg/dL (7 mmol/L), 2-hour blood glucose ≥200 mg/dL (11.1 mmol/L) following oral glucose tolerance test, or symptoms of DM and a random blood glucose ≥200 mg/dL (11.1 mmol/L). In the absence of symptoms, elevated fasting or random blood glucose should be confirmed on a separate day. Using the later parameters, screening for T2DM should be directed toward children at risk. Risk factors include severe obesity, minority ethnic background (Native Americans, Japanese/Pacific Islanders, Mexican-American, and African-American), acanthosis nigricans, hypertension, family history of T2DM, and children born to mothers with gestational DM (GDM). A high prevalence (>20%) of im-

paired glucose tolerance has been observed in a multiethnic group of obese children and adolescents, with obese African-American children having a 50% higher incidence of impaired glucose tolerance than obese Caucasian children.[51] Children of mothers with GDM have a higher incidence of T2DM compared to non-GDM, 19.3% versus 2.5%, respectively.[52-54] High-risk children and adolescents should undergo formal testing to rule out diabetes every two years starting at age 10 years old, or at the onset of puberty, or as symptoms develop.

PREVENTION

The benefits of lifestyle modifications in preventing or delaying the progression to T2DM in adults with glucose intolerance have been reported in several studies.[55,56] The Diabetes Prevention Program trial has shown that a comprehensive individualized lifestyle modification program (i.e., improvement of diet, increase in physical exercise, and smoking cessation) lowered the risk for development of T2DM by 58% compared with placebo and was equally beneficial to all patients, regardless of ethnicity, body mass index, sex, or level of glycemia.[55] Treatment with metformin was also effective but to a lesser extent than lifestyle modifications, resulting in a 31% reduction in risk of T2DM compared with placebo.[55] Similarly, the Finnish Diabetes Prevention Study assessed the efficacy of an intensive diet and exercise program in preventing or delaying T2DM in overweight individuals with impaired glucose tolerance.[56] When individual dietary advice aimed at reducing weight, increasing dietary fiber, and decreasing intake of saturated fat was combined with individual guidance to increase level of physical activity, several positive indications resulted: significantly greater reductions in weight, 2-hour plasma glucose, fasting and 2-hour plasma insulin, systolic and diastolic blood pressure, and serum triglycerides than a control group who received general information regarding the benefits of weight reduction, physical activity, and healthy diet for the prevention of diabetes. These studies support the benefits of lifestyle modifications in preventing or delaying the onset of diabetes in high risk adults. Replication of the interventions with youth and their families are needed to determine whether the benefits achieved in adult populations are transferable to children.

Table 1. Injectable Insulin Products

GENERIC (Legend)	ONSET (hr)	PEAK (hr)	DURATION (hr)
Lispro (Humalog)	0.25–0.5	0.5–1.5	4–6
Aspart Insulin (Novolog)	0.25–0.5	1–3	3–5
Regular Insulin (Humulin R, Novolin)	0.5–1	2–3	8–12
Isophane insulin (NPH; Novolin N, Humulin N)	1–1.5	4–12	24
Insulin zinc (Humulin Lente)	1–2.5	8–12	18–24
Prompt zinc insulin (PZI)	4–8	14–24	36
Extended insulin zinc (Ultralente)	4–8	16–18	>36
Insulin glargine (Lantus)	1–2		24
Insulin combinations:			
Humulin 70/30	0.25–0.5	2–12	24
Humulin 50/50	0.25–0.5	2–12	18–24
Novolin 70/30	0.5	2–12	24
Humalog 75/25	0.25	1–6.5	18–26
Novolog 70/30	0.25–0.5	0.5–6	18–24

THERAPEUTIC MANAGEMENT METHODS

Diet, exercise, and weight loss are the cornerstone of any treatment regimen and must be reinforced throughout the entire course of the disease. Weight loss and exercise improve glycemic control in obese T2DM children by decreasing glucose production and increasing muscle sensitivity to insulin.[57-61] Unfortunately, as the sole method of treatment, diet and exercise have limited success in the long-term management of adults with T2DM and are likely to be no more effective in children and adolescents.[62,63] Nonetheless, investigations regarding the type and duration of exercise on the magnitude of glycemic control and insulin sensitivity are needed. Children appear to have a more overt disease course compared to the more insidious onset in adults. They have a shorter latency period and have more acute symptoms at presentation (20–25% with DKA or severe ketonuria), suggesting that children with T2DM have a more aggressive disease than that which occurs in adults. Therefore, pharmacological treatment is necessary in the majority of children diagnosed with T2DM. Effective pharmacological therapy may target insulin production, insulin action, hepatic gluconeogenesis, or a combination of these factors. Four classes of pharmacological agents are available for the treatment of T2DM (Tables 1 and 2). These agents include insulin, insulin-sensitizing agents, insulin-stimulating agents, and glucose absorption inhibitors. Each of these classes of agents possesses a different mechanism of action enabling the agents to be used either alone or in combination.[64-66]

Insulins. Insulin is approved for use in children with T2DM and, until recently, was the only

Table 2. Oral Drugs for the Treatment of Type 2 Diabetes Mellitus

Drug	Usual Adult Dosage	Comments
Insulin Sensitizing Agents		
Metformin (Glucophage)	1500–2550 mg divided	Approved for use 10 to 16 yr, begin 500 mg twice daily, use lowest dose that controls blood glucose XR is not approve for use in children
Metformin XR	1000–2000 mg once or twice daily	
Pioglitazone (Actos)	15–45 mg once daily	Periodic Liver and kidney testing is required. Caution if creatinine >1.4 in women or >1.5 in men.
Rosiglitazone (Avandia)	4–8 mg once daily or divided	
Insulin Secretagogues		
Chlorpropamide (Diabinese)	250–375 mg once daily	Weight gain and hypoglycemia are side effects of all sulfonylureas, specifically glyburide due to its receptor high affinity. Take 30 min. before meals. Glipizide should be taken on empty stomach. Disulfiram-like syndrome. Syndrome of inappropriate secretion of antiduretic hormone (SIADH). Periodic liver function testing is required. Caution with drugs metabolized by CYP450. Caution heart failure patients.
Tolazamide (Tolinase)	250–500 mg once or twice daily	
Tobutamide	1000–2000 mg divided	
Glimepiride (Amaryl)	1–4 mg once daily	
Glipizide (Glucotrol)	10–20 mg once daily or divided	
Glyburide (DiaBeta, Micronase, Glynase)	5–50 mg once daily or divided	
Nateglinide (Starlix)	60–120 mg three times daily before meals	
Repaglinide (Prandin)	1–4 mg three times daily before meals	
Glucose Absorption Inhibitors		
Acarbose (Precose)	50–100 mg three times daily with meals	Increase dose slowly to decrease GI effects. Dose based on weight. Caution with liver or kidney problems.
Miglitol (Glyset)	50–100 mg three times daily with meals	
Combinations		
Metformin/glyburide (Glucovance)	250 mg/1.25 mg, 500 mg/2.5 mg, 500 mg/5 mg twice daily	See above comments for each drug Maximum dose is 2000 mg/20 mg divided twice daily
Metformin/glypizide (Metaglip)	250 mg/2.5 mg, 250 mg/5 mg, 500 mg/5 mg twice daily	
Metformin/rosiglitazone (Avandamet)	500 mg/1 mg, 500 mg/2 mg, 500mg/4 mg twice daily	Not for patients >80 years old.

agent approved for its treatment in children. The use of insulin has an important role in the early restoration of euglycemia in patients with new onset DM and who also have significant hyperglycemia. High glucose concentrations present a state of glucose toxicity to the pancreatic beta cells, resulting in decreased insulin production in the face of increasing insulin resistance and requirements. Short-term intensive insulin therapy to normalize blood glucose levels improves peripheral insulin sensitivity, restores pancreatic β-cell function, decreases hepatic gluconeogenesis, and can improve the subsequent response to oral antidiabetic therapy.[67-69]

Table 1 describes the rapid, short-acting, intermediate, and long-acting forms of insulin (including recombinant insulin analogs) with regard to the onset of action, peak, and duration of action. Commercial regular insulin exists as a hexamer (six molecule aggregates); after subcutaneous injection, the hexamer dissociates into dimers and monomers before significant absorption can occur. The short-acting insulins are derived from recombinant technology (Humolog, Novolog) or animal sources (Regular Ilente II) and is given 30 to 60 minutes before a meal to control the post-prandial glucose level.

The newer rapid acting insulins, lispro and aspart, differ from regular insulin by either transposing the amino acids at the 28 (proline) and 29 (lysine) positions on the insulin b chain (lispro) or by replacing proline at position 28 with aspartate (aspart). The modification in the β chain results in an insulin product that has fewer tendencies to self-associate into hexamers like regular insulin; therefore, the resulting insulin product is more rapidly absorbed into the bloodstream. The rapid-acting analogs just mentioned can be given within 15 minutes of a meal to control the post-prandial rise in blood glucose.

Intermediate-acting insulin is a suspension of zinc insulin crystals and protamine sulfate (isophane insulin, NPH and Lente). These insulins are usually given twice daily and are often given in combination with a rapid- or short-acting insulin. Long-acting insulins (extended insulin zinc suspension) are made by varying the concentration of zinc and protamine. The long-acting insulins are slowly absorbed with a peak at 16–18 hours and provide a basal level of insulin in the blood in an attempt to approximate the amount of insulin circulating in the body when not stimulated by glucose. A long-acting form of insulin has also been produced by modifying the α chain, replacing glycine with asparagine at position 21, and adding arginine at positions 31 and 32 of the β chain (glargine). This modification increases the stability of the hexamer structure, causing slower dissociation into dimers and monomers which results in slower absorption of insulin from the injection site. For ease of administration, some fixed combinations of NPH and regular or rapid-acting insulin are available as 70/30, 50/50, and 75/25 mixes. Insulin types are usually chosen according to their ability to achieve the best blood glucose control possible based on home glucose monitoring. The most common side effects are hypoglycemia, injection site reactions, and weight gain.[70] Patient education is needed regarding injection technique and timing, rotation of injection sites to avoid lipodystrophy, mixture and storage of insulin, home glucose monitoring, and treatment of hypoglycemia.

Insulin Stimulating Agents. There are two types of insulin secretogogues, the sulfonylureas (of which there are two generations) and nonsulfonylureas, neither of which has been adequately tested in children. The first generation sulfonylureas include tolbutamide, chlorpropamide, and tolazamide; second generation sulfonylureas agents include glyburide, glipizide, and glimepiride.[71] The principle mechanism of action of the sulfonylureas is the stimulation of insulin secretion from the pancreatic β-cell in response to glucose.[72] These agents may also suppress hepatic gluconeogenesis by increasing portal insulin, which reduces fasting plasma glucose and improves peripheral tissue sensitivity to insulin.[73,74] An additional effect reported with glimepiride is the partial restoration of the first phase of insulin secretion, resulting in a more physiologic response.[75,76]

Most adverse events are mild and reversible upon drug withdrawal. Hypoglycemia is the most important adverse effect and occurs more commonly with the longer acting agents such as glyburide. Insulin stimulating agents also cause hyperinsulimemia, which is associated with microalbuminuria, arteriosclerosis, hypertension, and weight gain. These agents have no effect on plasma lipid levels.

Repaglinide and nateglinide are nonsulfonylurea agents that stimulate insulin secretion.

In contrast to sulfonylureas, they cause a prompt short-lived burst of insulin that raises plasma insulin for 1 to 2 hours.[77] These agents are taken within 30 minutes before each meal. The drug is usually started at the smallest dose with dosage titration occurring at weekly intervals until the desired glycemic control or the maximum recommended dose is achieved. The major side effect is hypoglycemia. Repaglinide and nateglinide may also cause weight gain, though usually less than that observed with sulfonylureas. Similar to the sulfonylureas, these agents have no effect on plasma lipids.

Insulin Sensitizing Agents. The two major classes of insulin-sensitizing agents are the biguanides and the thiazolidinediones. Metformin is the only biguanide available for clinical use and has no effect on pancreatic β-cell insulin secretion.[78] The mechanism of action by which metformin improves insulin sensitivity is not fully understood. Recent work suggests that metformin acts on the AMP protein kinase pathway to enhance GLUT4 translocation and glucose uptake in hepatic and peripheral tissue.[79] Metformin decreases hepatic glucose production and likely inhibits hepatic glycogenolysis.[80,81] Fasting and postprandial insulin levels decline as a normal pancreatic compensatory mechanism for improved tissue sensitivity to insulin.[80,81] Metformin reduces cardiovascular risk factors by suppressing the release of fatty acids and lipid oxidation (which also enhances glycemic control) leading to a reduction in triglycerides, very low-density lipoprotein (VLDL), and total cholesterol, as well as a decrease in plasminogen activator inhibitor-1 (PAI-1) levels. Metformin, but not sulfonylurea therapy, was associated with a significant reduction in macrovascular complications, myocardial infarction, and stroke in the United Kingdom Progressive Disease Study.[82] Metformin appears to be unique in promoting weight loss, whereas other oral glycemic agents and insulin promote weight gain. Metformin is the only oral agent in which there is appreciable experience in the treatment of children and adolescents with T2DM and is FDA approved for use in children greater than 10 years of age.[83] The usual starting dose of metformin is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg per day, given in divided doses.

The most common side effects with metformin are gastrointestinal, including abdominal discomfort and diarrhea. These side effects tend to be transient and can be minimized by slow titration of the dose. Because metformin does not increase insulin secretion, hypoglycemia is a rare side effect. The most serious side effect is lactic acidosis, which occurs with a frequency of about 3 cases per 100,000 patient years. Avoiding metformin use in patients with other serious medical disorders including renal dysfunction, cardiogenic or septic shock, pulmonary insufficiency, and severe liver disease can reduce the risk for lactic acidosis.

The thiazolidinediones include rosiglitazone, pioglitazone, and troglitazone, the latter having been removed from the market because of hepatotoxicity. Most of our knowledge from this class of agents comes from the study of troglitazone. Thiazolidinediones improve tissue and liver sensitivity to insulin by binding to the peroxisome proliferator activated receptor (PPARg), a nuclear receptor whose highest level of expression is in adipocytes and intestinal cells and has very low levels of expression in other tissues, including muscle.[84-89] These agents decrease free fatty acid concentrations, and pioglitazone lowers plasma triglyceride concentration.[90] Thiazolidinediones increase fat cell numbers, accounting for the weight gain reported with the use of these agents, which is even greater when used in combination with insulin or a sulfonylurea.[91] About 2% of diabetic patients treated with troglitazone had an increase in serum liver enzyme levels. Liver disease is under close scrutiny for both rosiglitazone and pioglitazone, but no studies have found the development of increased levels of liver enzymes to be different from placebo. Edema has been reported in 2-4% of patients treated with thiazolidinedione monotherapy, 4-6% in patients on combination therapy with a sulfonylurea, and 10-15% in patients on combination therapy with insulin. This class of drugs should be avoided in patients with significant underlying heart disease.[92]

Glucose Absorption Inhibitors. The glucose absorption inhibitors are α-glucosidase competitive inhibitors of the brush border enzymes (maltase, isomaltase, sucrase, and glucoamylase) that break down oligo- and disaccharides into monosaccharides.[93,94] The available agents acarbose, miglitol, and vaglibose delay digestion

of complex carbohydrates within the gastrointestinal tract, leading to reduced glucose absorption and the postprandial rise in blood glucose levels.[93,94] These agents do not cause carbohydrate malabsorption. Rather, they retard the entry of glucose into the systemic circulation, allowing the pancreatic β-cell more time to increase insulin secretion in response to the blunted rise in plasma glucose. α-Glucosidase inhibitors appear to also improve insulin sensitivity by reducing the effect of glucose toxicity and cause a modest decline in plasma triglyceride levels without affecting LDL or HDL cholesterol.[95,96] No effect on weight has been observed. A limitation to the use of these agents is gastrointestinal side effects, including abdominal bloating, abdominal discomfort, diarrhea, and flatulence, which have been reported as high as 80%.[97] Starting with a small dose and slowly increasing the dose over several weeks can reduce gastrointestinal toxicity.

Combination Therapy. Only about 25% of adult diabetic patients achieve adequate glycemic control on monotherapy. In many patients, the use of two or more oral agents with differing mechanisms of action may result in additive effects. Furthermore, diabetes is a progressive disease, and the majority of patients will eventually require the addition of a second drug to achieve acceptable glycemic control. The additive glucose lowering effect has been seen with a number of combination therapies, including metformin/sulfonylurea, thiazolidinedione/sulfonylurea, and α-glucosidase inhibitor/metformin or sulfonylurea. Commercially available combination products are listed in Table 2. If the combination of two oral agents is not effective, a third agent, bedtime NPH or glargine insulin, or multiple daily injections of insulin can be used to improve glycemic control.[98] Continuous subcutaneous insulin infusion (through the use of an external insulin pump) may also be prescribed under these circumstances.

SUMMARY

T2DM constitutes an emerging epidemic in children, and it predominates in minority racial children. A number of intervening factors are contributing to the rise in the incidence of T2DM, including dietary and sedentary lifestyle habits that have lead to dramatic increase in the prevalence of obesity. There has been tremendous progress in the phamacologic management of adult T2DM with the introduction of a number of new classes of agents. Only recently have these newer agents undergone clinical testing in children. At the present time, only insulin and metformin are approved for use in children although many of the newer agents are currently undergoing clinical study in children. It will be important to understand which agent or combination of agents is optimal for children. The growing incidence of T2DM in children presents an enormous challenge to provide earlier diagnosis, methods of prevention, and effective treatment.

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REVIEW ARTICLE

The Role of Pamidronate in Pediatric Patients with Severe Osteogenesis Imperfecta

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Osteogenesis imperfecta (OI) is a heritable bone disorder with clinical features that include bone fragility, blue sclerae, and short stature. There are four main subtypes of OI, encompassing a wide range of clinical severity. The majority of patients have mutations in either the *COL1A1* or *COL1A2* gene that ultimately lead to an abnormal synthesis of or a decrease in the production of collagen. Bisphosphonates have been used effectively in adults and children to treat other bone disorders, since they have been proven to increase bone density through inhibition of bone resorption. Recent studies have demonstrated the advantages of pamidronate therapy in the treatment of children and adolescents with the more severe forms of OI. Pamidronate consistently increases bone mass, vertebral growth, and quality-of-life while decreasing the number of fractures in children with severe OI. Long-term effects are promising, and benefits of pamidronate therapy appear to outweigh the possible risks.

KEYWORDS: pamidronate, osteogenesis imperfecta, pediatrics

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ABBREVIATIONS: BMD, bone mineral density; COL1A1, proalpha1(I)-chain; COL1A2, proalpha2(I)-chain; hGH, Human growth hormone; NTX, N-telopeptide of type 1 collagen; OI, Osteogenesis imperfecta; Pi, serum inorganic phosphorus; PTH, parathyroid hormone; TRAcP, tartrate-resistant acid phosphatase; 25-OHD, 25-hydroxyvitamin D; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin

INTRODUCTION

Osteogenesis imperfecta (OI) is a congenital disorder caused by abnormal synthesis of collagen.[1,2] OI is classified into four distinct types depending on severity and clinical features and is characterized primarily by bone fragility, but clinical features can also include blue sclerae, short stature, skeletal deformities, and dental abnormalities. Children with OI were often mistaken for victims of abuse due to multiple or recurrent fractures.[3] However, as the awareness of OI has grown, so has the ability to differentiate between OI and child abuse. Very few treatment options are available to treat OI, and previously, medical treatment had not been very effective in altering the course of the disease, especially in those patients with severe forms of OI.[4] Recent studies have shown bisphosphonates to be beneficial by increasing bone mass in children with OI. This review focuses on the role of pamidronate, an aminobisphosphonate, in the treatment of the more severe forms of OI (primarily types I, III, and IV) in pediatric patients.

EPIDEMIOLOGY

OI occurs in all racial and ethnic groups. Its incidence in the United States is about one in 20,000 births, which includes children diagnosed up to 1 year of age.[3] This number does not include those children with milder forms of the disease that are not diagnosed until later in life; therefore, the incidence could theoretically be much higher than reported.

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CLASSIFICATION AND CLINICAL PRESENTATION

Sillence et al. developed the classification system for OI that is most commonly used today.[1,2] OI is divided into four subgroups depending on its clinical presentation (Table 1).[5] The severity of the disease can range from very mild to very severe. Type I is the most common form of OI and generally presents without any major deformities. Type II OI is always lethal in the perinatal period; therefore, studies pertaining to the treatment of this type of OI are not available. Children with types III and IV OI generally present with short stature, difficulty ambulating, and are more prone to deafness than those with type I; they also represent the group most commonly requiring medical and surgical treatment.

Since type IV OI includes patients who do not fit into any of the other categories, this group represents a heterogeneous group of patients.[6-9] Extensions of the current classification system were later proposed to include types V, VI, and VII; however, a universal classification system for these types has not been officially adopted due to the small number of patients afflicted. These patients were originally classified as having type IV OI, but they share unique characteristics that could distinguish them from other type IV patients. Types V and VI have clinical features different from patients with type IV and do not involve collagen type I mutations.[6,7] Type VII can be distinguished from the other types based on the fact that it is an autosomal recessive disorder localized on a chromosome different from the loci for collagen type I.[8,9] Other features of OI include increased bruising, hypercalciuria, nephrocalcinosis, skeletal fractures, scoliosis, ocular defects (keratoconus and retinal detachment), hydrocephalus, compression of the cervical spinal cord, peripheral weakness, and loss of bladder control.[1,2,5] Osteoporosis progresses with age. Bone mineral density (BMD) T-scores range from –2.5 to –4 at the proximal femur or lumbar spine by dual-energy x-ray absorptiometry (DEXA).[5]

ETIOLOGY

OI is caused by mutations in one of two genes, *COL1A1* and *COL1A2*, which code for the proalpha1(I)-chain and proalpha2(I)-chain, respectively, of procollagen type 1.[5] Procollagen type 1 is the precursor to collagen type 1, the major structural protein found in most connective tissues. Collagen type 1 is abundant in bone, tendon, and ligament, but it can also be found in the lungs, dentin, and sclerae.

OI presents as an autosomal dominant trait but sporadic mutations can also occur.[1,2,5] Mutations in the biosynthesis of collagen type 1 result in a decrease in the amount of collagen type 1 produced or an increase in the production of defective collagen.[4,10] In type IA OI, only the normal *COL1A1* allele is expressed. The mutant

Table 1. Classification of Osteogenesis Imperfecta[1-3,5]

TYPE	BONE FRAGILITY	CLINICAL FEATURES	SCLERAE
I (50%*)	Mild to moderate	IA Normal stature; onset of fractures after birth; no major skeletal deformities; presenile hearing loss; compression of posterior fossa in 10%; triangular facial shape with mandible narrowed anteriorly IB Similar to IA but with dentogenesis imperfecta; may be shorter in stature	Blue
II (5%*)	Very severe	Lethal in the perinatal period; multiple fractures at birth; severely deformed	Dark blue
III (20%*)	Moderate to severe	Extremely short stature; fractures at birth with progressive deformity; not usually ambulatory; severe osteoporosis; occasional deafness	White to blue
IV (25%*)	Mild to severe	IVA More severe than IA; variable stature; usually ambulatory but with mechanical support; patients who do not fit into any of the above categories; occasional deafness IVB More severe than IB; similar to IVA but with dentogenesis imperfecta	White to gray

** Frequency*

COL1A1 allele codes for premature termination codons but translation is stopped via a quality control process. The synthesis of collagen type 1 is reduced by approximately 50 percent, but otherwise normal proteins are produced. In the more severe forms of OI (types IB, II, III, and IV), expressed mutations in *COL1A1* or *COL1A2* give rise to a structural alteration of collagen type 1. The repeating amino acid sequence Gly–X –Y (where X and Y is any amino acid) of the triple helical domain of the collagen chain is often affected, most commonly by a substitution of the glycine component. Both types of mutations are detectable in approximately 80 to 90 percent of patients with OI.[10] The cause of OI in the remaining cases is unclear.

OI versus *CHILD ABUSE*

Victims of child abuse often present with skeletal fractures.[3] As many as 100,000 children under the age of five have been physically abused, approximately 30% of whom have presented with fractures.[11] For years, children with OI have been mistaken for victims of abuse; therefore, OI is now included in the differential diagnosis of child abuse. The two are distinguished from each other by characteristic physical features, family history, and fracture type. However, atypical findings may make it difficult to differentiate OI from abuse. Analysis of the synthesis of collagen from cultured dermal fibroblasts may be beneficial in identifying patients who could potentially have OI, even in milder forms of the disease. This test has been investigated as a means to distinguish cases of OI from suspected child abuse. One study found that many patients with other indicators of OI had normal collagen studies (15%) while a small percentage of patients with indicators suggesting abuse may present with abnormal collagen studies. Because of the implications associated with a false positive result (presumed OI when there may be abuse) or false negative result (presumed abuse), studies of collagen biosynthesis should only be conducted in those children whose physical and radiologic findings lead to an uncertain diagnosis. Once the diagnosis of OI is confirmed, the decision of what therapeutic option to pursue becomes very important.

TREATMENT WITH HUMAN GROWTH HORMONE

The pharmacotherapeutic options for OI are limited to very few drugs. Human growth hormone (hGH) is believed to increase collagen type 1 synthesis by stimulating the expression of insulin-like growth factor I and insulin-like growth factor binding protein-3.[12] Treatment with hGH may be beneficial in increasing bone density and growth velocity in children with mild type I disease. However, there is a possibility that the use of hGH in some patients may be associated with an increased risk of fractures.[13] Thus, alternate therapy may be needed to help those with more severe forms of OI.

MECHANISM OF ACTION AND SIDE EFFECTS OF BISPHOSPHONATES

Bisphosphonates have been used extensively to increase bone density and decrease bone resorption in adults, and are used to treat conditions such as osteoporosis and Paget's disease.[14] Currently, the only FDA-approved indications for pamidronate are for the treatment of hypercalcemia of malignancy, osteolytic bone metastases of breast cancer, osteolytic lesions in multiple myeloma, and moderate to severe Paget's disease of bone.[15] While not FDA-approved for use in children, these compounds have also been used in pediatric patients to treat a number of other disorders with good results (Table 2).[16]

Bisphosphonates work by inhibiting normal and abnormal bone resorption. Bisphosphonates can be broken down into two groups —those that do not contain nitrogen (e.g., etidronate and clodronate) and those that do (e.g., alendronate, risedronate, and pamidronate).[17] The mechanism of action for the non-nitrogen containing bisphosphonates is believed to involve the production of toxic analogs of adenosine triphosphate that lead to osteoclast apoptosis. Alternatively, nitrogen-containing bisphospho-nates inhibit the synthesis of farnesyl pyrophosphate in the mevalonate pathway.[17,18] This potentially leads to the inhibition of protein isoprenylation, resulting in osteoclast apoptosis and inhibition of osteoclast-mediated bone resorption. However, since some studies suggest that osteoclast apoptosis does not occur, this aspect of the

mechanism of action remains controversial.[19]

An "acute-phase reaction" is commonly seen during the first cycle of intravenous bisphosphonate therapy.[20] This reaction presents with an increase in body temperature and bone pain, but it does not seem to recur with subsequent infusions. Nausea and vomiting may also occur;[15,21] some patients may benefit from pretreatment with ondansetron.[22]

USE OF PAMIDRONATE IN OI

Several studies have demonstrated the advantages of using bisphosphonates in children and adolescents with OI, especially those afflicted with deforming types (types III and IV, and severe cases of type I). Glorieux et al. conducted a non-controlled, observational study that followed 30 children, ages three to 16 years (mean±SD; 9±4years), with severe OI (type III and IV).[20] Pamidronate (mean±SD; 6.8±1.1 mg/kg/year) was administered over three successive days by slow, intravenous infusion at four to six month intervals for 1.3 to 5.0 years (mean=765 days).

Bone density, measured by DEXA of the lumbar spine, increased significantly by a mean of 41.9±29%.[20] The z-score, which corrects bone density measurements for age, improved from –5.3±1.2 to –3.4±1.5 (P<0.001). Cortical width of the metacarpals increased significantly compared to pretreatment values and persisted for up to two years of treatment. The number of fractures decreased significantly (2.3±2.2 to 0.6±0.5 per year, P<0.001). Alkaline phosphatase, a measure of bone resorption and formation, decreased slightly but significantly from baseline (mean±SD; 13±8 %/year) while N-telopeptide of type 1 collagen (NTX), a marker of bone resorption, decreased to a greater degree (26±17 percent per year; P<0.001). The mean growth rates of the ten prepubertal children and the eleven children undergoing puberty increased following treatment but results were not statistically significant (P=0.16 and P=0.11, respectively). Pain and ambulation also showed improvement after pamidronate therapy but results were considered to be fairly subjective. An acute-phase reaction was seen in 26 of the patients but this reaction did not recur with repeated infusions. Although the study was non-controlled, the improvements seen in the patients were believed to be due to pamidronate therapy. However, long-term effects and the limits to the benefits of therapy are still unknown.

The previous study was extended to include children <3 years of age.[23] Nine patients ranging in age from 2.3 to 20.7 months (mean±SD; 10.7±4.5 months) with severe OI (type III and IV) were initially given pamidronate every four months. However, since infants experience a more rapid bone turnover and growth compared to older patients, the interval between treatments was decreased to six to eight weeks. Pamidronate was administered in a manner similar to the previous trial with cumulative doses averaging 12.4 mg/kg/year. The results were compared with six historical controls that also had severe OI but received no pamidronate therapy.

Where BMD z-score increased in the pamidronate group, a significant decrease in BMD was observed in the control group (P=0.02).[23] Other similar benefits to the previous study included decreased pain and improve-

Table 2. Indications for the Use of Bisphosphonates in Children[16]

Fibrodysplasia ossificans	Myositis ossificans
Fibrous dysplasia	Oxalosis
Gaucher type 3	Antenatal pamidronate for maternal hypercalcemia
Hypercalcemia	Familial idiopathic hyperphosphatasia
Idiopathic infantile aortic calcifications	Juvenile chronic arthritis
Juvenile osteoporosis	Calcinosis of dermatomyositis
Osteogenesis imperfecta	Congenital neutropenia treated with GCSF
Osteopenia (cerebral palsy, paraplegia)	Steroid-induced osteoporosis

Adapted from reference 16 with permission

ments from baseline in vertebral area and fracture rate (2.6±2.5 vs. 6.3±1.6 per year in controls, P< 0.01) following 12 months of therapy. Side effects included transient hypocalcemia and hyperparathyroidism but the clinical significance of this remains unclear. Overall, children between 2 and 20 months of age with severe OI also experienced clinical and radiological improvements. However, the study did not evaluate the optimal length of treatment, and safety following long-term use remains undetermined.

In one of the few studies conducted in the United States, six children with OI received pamidronate according to the protocol described above by Glorieux et al.[24] When compared to baseline values, patients experienced a mean improvement in BMD of 48% with an average increase in z-score of 1 (range: 0.5–1.4, P<0.03). The number of fractures and the improvement in functional status could not be systematically evaluated due to the fact that increased mobility often led to more injuries. This study independently confirmed the results of Glorieux et al. that cyclic administration of pamidronate is beneficial in increasing BMD and physical activity.

Rauch et al. also analyzed the effects of pamidronate therapy on the bone tissue of children and adolescents with more severe forms of OI (types I, III, and IV) in order to determine the histological basis for the increase in BMD in these patients.[19] The study included 45 patients, ages 1.4 to 17.5 years (mean±SD; 8.4±4.3 years), who received pamidronate for one to four years. The dosing regimen was dependent on the age of the patient (Table 3). Iliac bone biopsies before and after approximately two years of treatment were obtained from alternate locations and then compared with those of two control groups: patients with OI who had not received any bisphosphonate therapy, and patients with no metabolic bone disease.

Patients experienced comparable increases in BMD and decreases in markers of bone resorption (NTX) compared to similar studies.[22] Cortical width increased by 88% (P< 0.001) and cancellous bone volume increased by 46% (P=0.006), representing an increase in trabecular number compared to pretreatment values.[19] Neither change was significantly associated with the duration of pamidronate therapy. Trabecular thickness did not significantly increase (P=0.10). An important delay in bone mineralization lag time was demonstrated compared to pretreatment values (P=0.002) and versus OI and healthy controls (P=0.002 and P=0.001, respectively). Overall, mineral apposition rate was not significantly different among any of the three groups, and osteoid thickness and percentage of bone surface actually decreased following pamidronate therapy. This is in contrast to what has been observed with the first generation bisphosphonate, etidronate.[17] The ratio of bone formation rate to bone surface decreased significantly in regions containing cancellous bone (P<0.001), indicating a decrease in cancellous bone remodeling.[19] Since remodeling does cause a transient structural weakness of bone tissue, a decrease in bone turnover may be beneficial. The long-term consequences of these structural changes on bone stability remain unclear. Therefore, these investigators recommended that cyclic administration of pamidronate in children with OI be used when clinical benefits outweigh potential long-term risks.

Microdamage in the tissue may accumulate over time, causing potential future problems. This was the case documented in a 12-year-old boy with pamidronate-induced osteopetrosis

Table 3. Pamidronate dosing schedule[19]

AGE* (yrs)	CYCLE LENGTH	CYCLE FREQUENCY	DOSE OF FIRST CYCLE (mg/kg/d)	DOSE OF SUBSEQUENT CYCLES (mg/kg/d)
< 2	3 days†	q 2 mo	Day 1=0.25 Days 2 and 3=0.5	0.5 for 3 days
2–3	3 days†	q 3 mo	Day 1=0.38 Days 2, 3=0.75	0.75 for 3 days
>3	3 days†	q 4 mo	Day 1=0.5 Days 2, 3=1	1 for 3 days

** all patients received adequate calcium and vitamin D intake according to the recommended daily allowance*
† consecutive days

(marble bone disease).[25] This patient did not have osteogenesis imperfecta, but had unexplained bone pain, fractures, idiopathic hyperphosphatasia, and thrombocytopenia. Following 2.75 years of treatment with pamidronate (>4 times the normal doses used in OI), this patient had evidence of osteopetrosis which included club-shaped metaphyses due to defective osteoclast activity, increased bone densiometry, elevated creatine kinase of the isoenzyme derived from bone cells (BB-CK), and elevated serum alkaline phosphatase (bone isoenzyme). Bone remodeling defects persisted in this patient for at least two years following the discontinuation of pamidronate therapy. Therefore, because of concerns related to impaired bone remodeling following large-dose pamidronate therapy, close monitoring of biochemical markers of bone remodeling is recommended in patients receiving long-term pamidronate therapy.

Rauch et al. also conducted another study of 165 patients (ages 2 weeks to 17.9 years) with severe OI (types I, III, and IV).[26] This study only focused on the effect of pamidronate on bone and mineral metabolism; it did not evaluate any beneficial effects that pamidronate may have on bone stability. The dosing regimen was identical to that of the authors' previous trial (Table 3). The study population was stratified into three groups according to age. The first group included children less than two years of age, the second group included children between the ages of two and three years, and the last group included children older than three years of age. Biochemical measurements included serum inorganic phosphorus (Pi), alkaline phosphatase, ionized calcium (Ca^{2+}), parathyroid hormone (PTH), tartrate-resistant acid phosphatase (TRAcP, an osteoclast enzyme), 25-hydroxyvitamin D (25-OHD), and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D]. They also measured creatinine (uCr), calcium (uCa) and NTX urine concentrations.

During the first three days of pamidronate therapy, serum Pi and Ca^{2+} decreased significantly from baseline in all age groups.[26] The decrease in Ca^{2+} did not cause clinical signs or symptoms of hypocalcemia in any of the patients, and Ca^{2+} levels returned to pretreatment results before the second treatment cycle. PTH levels increased considerably and were still significantly above baseline before the second cycle in patients less than two years of age ($P<0.01$). Serum concentrations of 25-OHD did not change during the three days of therapy, whereas 1,25-$(OH)_2$D levels doubled but returned to pretreatment values before the start of the second cycle. Urine calcium decreased significantly and was undetectable in 54 patients (35%) on the third day of the infusion cycle. All age groups experienced a significant decrease in uCa/uCr ratio after three days of treatment. Patients over three years of age still had a uCa/uCr ratio significantly below baseline before the second cycle ($P<0.05$). All age groups had a decrease in uNTX/uCr ratio ($P<0.001$), which remained significantly lower than baseline in all age groups at the start of the next cycle. The decrease in TRAcP was only significant in the oldest age group ($P<0.001$). The decrease in alkaline phosphatase was significant in all age groups ($P<0.001$) and continued to be lower than baseline before the start of the second cycle.

A subgroup analysis evaluated long-term effects in 40 patients who had started pamidronate therapy between 3–18 years of age and who were treated for at least four years.[26] Serum Ca^{2+} values did not change significantly over four years, but serum Pi decreased with time ($P<0.05$). PTH increased after two years ($P<0.01$) but remained stable and within reference ranges for the next two years. Serum levels of 25-OHD increased after the first year of therapy ($P<0.001$) but decreased steadily thereafter, whereas 1,25-$(OH)_2$D levels did not change. The uCa/uCr ratio decreased after two years of therapy but then stabilized. The uNTX/uCr ratio decreased during the first year ($P<0.001$) and continued to decrease slowly over the next three years. Serum TRAcP increased during the first two years ($P<0.05$) but returned to baseline values. Alkaline phosphatase values continued to decline steadily throughout the entire treatment period.

The most significant short-term effect of pamidronate therapy is the decrease in serum Ca^{2+} levels.[26] The authors recommended that patients maintain an adequate calcium intake to prevent serious effects of hypocalcemia, especially during the first infusion cycle. However, long-term Ca^{2+} concentrations remained unchanged. Because the uNTX/uCr ratio continued to decrease with long-term treatment with pamidronate, caution must be used because the effects of chronically low bone turnover in children are still unknown.

Zeitlin et al. analyzed both short- and long-term effects of cyclic intraveneous pamidronate on height and weight in a large group of children with severe forms of OI types I, III, and IV.[27] Patients received pamidronate as described in the previous trials.[20,23] Of the 125 eligible patients (0.04–15.6 years of age at baseline), 116 children were evaluated after one year of therapy and 41 children were evaluated after four years.[27] Rather than comparing patients with OI to healthy controls, the researchers used a regression analysis to determine the expected heights and weights for untreated patients with OI. Although there were few statistically significant changes in healthy population-based z-scores for height and weight in patients with OI (P=0.04, OI type III height only, P=0.01, OI type I weight only), all results were statistically significant (P<0.02) for height and weight when the percent change based on expected values were compared to baseline values after four years.[27] The only exception to this was the percent change in weight after four years for patients with OI type IV (P=0.05). An additional eight patients who achieved their final adult height during the study period also experienced a significant change in expected height compared to baseline when compared to predictions based on untreated patients (P=0.04). In conclusion, long-term cyclic pamidronate therapy has beneficial effects on height and weight based on expected growth patterns in untreated patients with similar types of OI.

Zacharin et al. conducted an open, observational study of 18 children (1.4–14.5 years) with types III and IV OI over a two year period.[28] This study not only investigated the effects of pamidronate, but it also evaluated the correlation between severity of the disease, age at onset of treatment, type of collagen mutation, and response to treatment. Similar to previous studies, treatment with pamidronate was effective in increasing BMD (124.7±75.7%) and vertebral height (68.5%) while decreasing the number of fractures. Although difficult to analyze statistically due to the heterogeneity of the population studied, all but two of the twelve patients with baseline disabilities who completed the studied experienced an increase in their mobility score (0 – bed or wheelchair bound, 4 – independent walking). All patients experienced a decrease in the number of fractures; however, the overall change in fracture rate could not be quantified. No significant correlation was found between the age at start of treatment and the response to treatment (r^2=0.14), most likely because the greatest benefits of pamidronate therapy on BMD were seen with the most severely affected patients. Side effects were minimal, although eight children experienced an acute-phase reaction. This study also found pamidronate to be safe and effective in treating children with severe OI, but long-term effects were not evaluated.

In one of the few long-term studies, 28 patients (0.6–18 years of age) with mild to severe OI received monthly infusions of pamidronate (10–40 mg/m^2) for two to nine years.[14] No adverse effects were noted with the exception of acute-phase reactions in five of the patients. The benefits of pamidronate therapy were consistent with findings from the other studies. Pamidronate may therefore be considered relatively safe and effective for long-term use for the treatment of OI.

Five separate case studies involving a total of 22 children have also concluded that cyclic pamidronate therapy is beneficial in patients with severe OI.[22,29-32] Nineteen patients received intravenous pamidronate in doses ranging from 2–14.4 mg/kg/year divided every six months to monthly, and three patients received 120–360 mg/m^2/year in monthly intervals. Two case series evaluated the benefits of oral pamidronate for the treatment of OI. One patient received oral pamidronate, 250 mg daily, for two months alternating with a two-month drug free interval.[33] Three boys (ages 1, 1.7 and 6 years) with OI type III received either 5 mg or 10 mg of oral olpadronate (a European name for pamidronate) per day.[34] All of the patients in these studies were treated for one to seven years. Significant increases in BMD, decreases in number of fractures and pain, and a relatively safe short-term side effect profile were consistently seen in each of the studies. There is a possibility that pamidronate is more effective in younger patients, but there is not enough data to support this since the study population was very small.[29] Also, the rate of fractures decreased less dramatically in one of the studies, possibly because the researchers used a dose smaller than previously studied.[34] The limited data available using oral pamidronate therapy suggest that patients unable to receive or tolerate parenteral therapy may

respond to oral therapy. Caution should be exercised, however, because the optimal oral dosing regimen has yet to be determined.

Other potential, yet unproven, benefits of pamidronate therapy include as increase in the success of surgical disease management.[28] In one study, surgeons reported decreased complications (delayed bone union, rod dislodgement) following intramedullary rodding in patients receiving pamidronate. Patients also reported less perioperative pain compared with previous procedures but this also has not been systematically evaluated.

SUMMARY

Children with the more severe forms of OI (mainly types III and IV) need prompt initiation of therapy to prevent further disabilities. Although treatment options are limited, the use of bisphosphonates such as pamidronate has proven to be beneficial. Pamidronate is recommended in children with severe OI because it has consistently been shown to increase bone mass, vertebral growth, mobility, and quality of life while decreasing the incidence of fractures. While there is a potential for impairment of bone remodeling when used at high doses, overall, long-term effects of pamidronate are promising, and the benefits of its use in children with moderate to severe disabling as a result of OI outweigh the possible risks.

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JPPT

CLINICAL INVESTIGATION

Intraventricular Vancomycin In Pediatric Patients With Cerebrospinal Fluid Shunt Infections

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OBJECTIVES To determine: 1) the range and magnitude of vancomycin trough cerebrospinal fluid (CSF) concentrations following intraventricular (IVT) vancomycin; 2) any correlation between patient demographic and CSF vancomycin concentrations; and 3) eradication and complications rates following IVT vancomycin.

METHODS Medical records of pediatric patients with shunt infection who received IVT vancomycin during a 12 month period were reviewed. Demographic, microbiological data, IVT/intravenous (IV) vancomycin dosing, concomitant antibiotics, CSF and serum vancomycin concentrations, and CSF drainage output were recorded.

RESULTS Seventeen patients ages 4 months to 17 years were hospitalized for shunt infection. *Staphylococcus epidermidis* (n=12) was the predominant organism. Sixteen patients received 10 mg, and one patient received 5 mg of IVT vancomycin for 3–23 days. All but one received concurrent IV vancomycin. The mean maximum trough CSF vancomycin concentration noted for 16 patients who recieved 10 mg of IVT vancomycin was 18.4±21.8 μg/mL (range: between 0.4 to 187.3 μg/mL). All four adolescents ≥25 kg had CSF vancomycin concentrations ≤5 μg/mL, three of four infants/children between 10.1 and 24.9 kg had trough CSF vancomycin concentrations between 10–20 μg/mL, and five of nine infants <10 kg had CSF concentrations >20 μg/mL. All organisms were successfully eradicated. One patient developed chronic eosinophilia presumed related to elevated CSF vancomycin concentrations (187 μg/mL).

CONCLUSIONS –The combination of IVT and IV vancomycin effectively eradicated CSF shunt infections. CSF vancomycin concentrations are highly variable and poorly correlated with age and CSF output. Following a 10 mg IVT vancomycin dose, CSF concentrations appear to be lower in older children and elevated in infants/young children. One infant experienced a complication related to an elevated CSF vancomycin concentration; hence, therapy must be individualized, using CSF trough vancomycin concentrations.

KEYWORDS: intraventricular, shunt infection, vancomycin

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INTRODUCTION

The preferred method for shunting cerebrospinal fluid (CSF) from the ventricles is via a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt. Infection is a major cause of shunt failure, which places the patient at risk of intellectual impairment, the development of loculated CSF compartments, and death. Although the incidence of post-operative CSF shunt infections varies considerably among centers, ranging from 1% to 39%,[1] most report infection rates of about 5%.[2] The most common causative pathogens include *Staphylococcus epidermidis* and *Staphylococcus aureus*. Recently, the emergence of methicillin-resistant strains of Staphylococcus has made vancomycin the antibiotic of choice for this infection.[3]

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While human data are lacking, animal data suggests that the central nervous system (CNS) lacks an active transport mechanism for vancomycin.[4] Also, researchers have reported that in the presence of meningeal inflammation, vancomycin penetration into the CNS is unreliable.[5] Although therapeutic CSF vancomycin concentrations and successful treatment of shunt infections have been reported following intravenous (IV) vancomycin alone,[6-8] the poor CSF penetration following systemic administration may result in failure to eradicate infection.[7-10] Additionally, the bactericidal and bacteriostatic activities, calculated as the ratios of the minimum bactericidal concentration and minimum inhibitory concentration to the CSF vancomycin concentration, were inadequate after three doses (15 mg/kg q 6 hours) of vancomycin.[11] Therefore, direct instillation of the drug into the CNS may be necessary to achieve CSF concentrations capable of successfully eradicating an organism.[12-16]

The purpose of this retrospective study was to evaluate the treatment and outcomes of patients with culture proven CSF shunt infections who were treated with IV and IVT (intraventricular) vancomycin. The objectives were to determine: 1) the range and magnitude of vancomycin trough CSF concentrations following IVT vancomycin; 2) any correlation between patient demographics and CSF vancomycin concentration; and 3) eradication and complications rates following the administration of IVT vancomycin.

METHODS

In order to identify potential patients, medical record discharge codes for shunt infections and neurosurgery records for patients with shunt infections were reviewed for all admissions between June 1999 and June 2000. Patients were included if they were between 0 and 18 years of age and had a VP or VA culture positive shunt infection that was treated with IVT vancomycin (5 or 10 mg) with or without systemic vancomycin (10–15 mg/kg/dose q 6 hours). The shunt was externalized if the patient had signs of peritonitis, evidence of tunnel track infection, septicemia, cor pulmonale, or if the shunt was malfunctioning.

An aspirate of CSF was obtained from the shunt and gram-stain: WBC with differential count, RBC, protein and glucose were determined. A neurosurgeon administered the IVT vancomycin over <2 minutes into the shunt or via the externalized shunt at a concentration of 5 mg/mL and the shunt was clamped for 1 hour. Depending on the particular neurosurgeon and infectious diseases service recommendations, IV vancomycin at dosages of 10–15 mg/kg/dose q 6 hours (maximum 2 gm/day) was given concurrent with IVT vancomycin. The following day, a CSF sample was collected and analyzed for WBC with differential count, RBC, protein, and glucose, and a trough vancomycin CSF concentration was obtained prior to the next dose. The clinical laboratory of our institution determined

Table 1. Patient Demographics

Patient	Gender	Age (yr)	Weight (kg)	ShuntType	Underlying Pathologies	Organism
1	F	14	61	VP	Spina bifida	SE
2	F	15	67	VP	Spina bifida	SE
3	M	16	117	VP	Paraencephalic cyst	GBS
4	M	6	19	VP	Intracranial tumor	SA
5	M	7	25	VP	Head trauma	SE
6	F	0.42	3.4	VP	Craniosynostosis	SE
7	F	3	12.8	VP	Unknown	SE
8	F	1.66	10	VP	IVH	SE
9	M	4	18	VP	Intracranial tumor	SA
10	F	1.58	10	VP	Aqueduct stenosis	SE
11	F	1.33	9.25	VP	IVH	SE
12	F	17	10	VP	IVH	SE
13	F	0.42	5.5	VP	Unknown	SE
14	M	0.33	3.3	VP	IVH	SE
15	F	4	15	VA	Anoxic brain injury	SE
16	M	0.75	6	VP	Fronto-nasal encephalocele	BS
17	M	0.8	9.6	VP	Congenital hydrocephalus	SA

VP, ventriculo-peritoneal; VA, ventriculo-atrium; IVH, intraventricular hemorrhage;
SE, *Staphylococcus epidermedis;* GBS, *Group B streptococcus;* SA, *Staphylococcus aureus;*
BS, *Bacillus species*

CSF vancomycin concentrations using a fluorescence polarization immunoassay (FPIA-AxSYM, Abbott Laboratories).

Although sterilization of the CSF has been achieved with a variety of CSF vancomycin concentrations, a concentration of 5 μg/mL showed slightly lower activity (not statistically significant) than concentrations of 10, 100, 300 μg/mL,[12] and a concentration of 2 μg/mL was significantly less bactericidal than a concentration of 5 μg/mL.[12] These authors contend that time-dose regimens that provide trough CSF vancomycin concentrations of 5–10 μg/mL provide maximal effectiveness. The above studies are the basis for our neurosurgeons' practice and are the reason we used of a trough CSF vancomycin concentration between 5 and 10 μg/mL in this study.

Each CSF vancomycin concentration was reviewed by the neurosurgeon, and the IVT dosage was adjusted as needed. If the trough vancomycin concentration was <20 μg/mL, the same dose of IVT vancomycin was injected the next day into the shunt or via the externalized shunt. If the concentration was >20 μg/mL, the IVT vancomycin was held, and another CSF sample was obtained in 24 hours. Fluid was extracted from the shunt each day and sent to the laboratory for microbiological assessment. Once three consecutive negative CSF cultures were reported, the patient's shunt was replaced or revised, and IVT and IV vancomycin were continued for an additional two days.

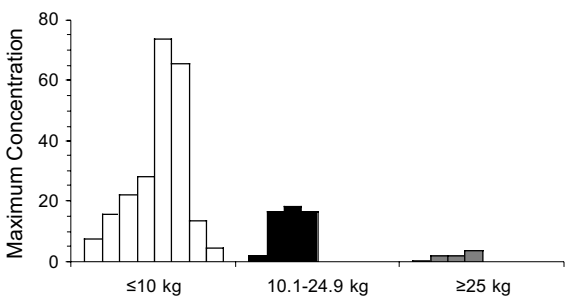
Patient demographic data including age, weight, gender, shunt type, and diagnosis requiring initial shunt placement were noted. Likewise, microbiological data, IVT/IV vancomycin doses, concomitant antibiotics, CSF and serum vancomycin concentrations, and CSF drainage output were recorded. Pearson correlation was used to assess the relationship between vancomycin CSF concentration and both age and CSF output. Statistical significance was set *a priori* at P ≤0.05, and all data are presented as mean±SD. Statistical analysis was performed using the MINITAB 13 statistical software (Release 13. Minitab, Inc.). The study was approved by the Institutional Review Boards of The University of Tennessee Health Science Center and Le Bonheur Children's Medical Center, and informed consent was deemed unnecessary.

RESULTS

Patient demographics are depicted in Table 1. Seventeen patients (10 females), mean age of 5.5±6.1 years (range: 4 months–17 years), weight of 23.6 ± 30.3 kg (range: 3.3–117 kg), were hospitalized for shunt infections. Sixteen patients had VP shunts, and the remaining one had a VA shunt. Underlying pathologies that required initial shunt placement varied; however, intraventricular hemorrhage, tumor, and spina bifida were the most predominant causes (Table 1). All patients had positive CSF cultures for *S. epidermidis* (n=12), *S. aureus* (n=3), *group B streptococci* (n=1) and *Bacillus species* (n=1) (Table1). Ninety-five percent of shunt catheters were externalized during IVT vancomycin therapy.

Sixteen patients received 10 mg/day of IVT vancomycin, while one patient (# 17) received 5 mg/day. The mean duration of IVT vancomycin therapy was 10.9±4.9 days but ranged from 3 to 23 days. The mean number of doses given during this time was 8.5±4.1 (range: 2–16). Trough CSF vancomycin concentrations were obtained prior to a dose in 17 patients across the duration of therapy and ranged from 0.4 to 187.3 μg/mL. If one excludes patient 17 whose vancomycin concentration was 187.3 μg/mL, the mean maximum CSF trough concentration was 18.4±21.8 μg/mL. All four adolescents ≥25 kg had CSF vancomycin concentrations ≤5 μg/mL (2±1.4; range:0.4–3.8 μg/mL), three of four infants/children between 10.1 and 24.9 kg had trough CSF vancomycin concentration between 10–20 μg/mL (13.5±7.7; range: 2–18.5–mg/L), and five of nine infants ≤10 kg had CSF vancomycin con-

Figure. Maximum CSF vancomycin concentration for each of the 17 patients.



Patient 17 not shown in this figure. Because the graph stops at 80 μg/mL, the actual concentration for patient 17 was 187.3 μg/mL.

centration >20 μg/mL (29.1± 26.3; range: 4.8–73.8 μg/mL) (Figure). Because patient 17 had an unusually high concentration (187.3μg/mL), which unduly influenced the ≤10 kg group, he was excluded from the above mean data. Daily CSF drainage outputs were available in fourteen patients and were averaged for the duration of their hospitalization (Table 2). Mean ± SD was 374.5 ± 246.23 mL/day (range: 44–1054 mL/day). Although there was a poor and non-statistically significant correlation between age (r^2=0.14; P=0.135) and maximum CSF trough concentration, there was a poor, but statistically significant correlation between CSF output and maximum CSF trough concentration (r^2=0.68; P=0.01). Hence, neither age nor CSF output could be used to predict trough CSF vancomycin concentration. These data are limited by the small sample size of our study.

Sixteen patients received concomitant IV vancomycin. Infants and children received a mean IV vancomycin dose of 54.6±9.1 mg/kg/day (range: 40–70 mg/kg/day), while adolescents received 2–3 g/day (Table 2). Eleven patients had trough serum vancomycin concentrations monitored, which ranged from 3.6 and 76.3 μg/mL. Patients 9 and 14 had elevated systemic vancomycin concentrations secondary to varying degrees of renal failure.

All organisms were successfully eradicated as evidenced by CSF cultures becoming sterile by a median of four days (range: 2–10 days). There were no complications from the administration of IVT vancomycin except for patient 17 who developed chronic CSF eosinophilia that was presumed related to a high CSF vancomycin concentration of 187.3 μg/mL.

Table 2. Treatment Outcomes

Pt	Days of IVT VAN (No. of doses)	CSF VAN-T Concentration* (Range)	Average CSF Output (mL/d)	IV VAN Dose† (days)	Serum VAN-T Concentration* (Range)	Concurrent Antibiotics	Negative CSF Culture (Days‡)
1	15 (9)	0.4§	259.2	2 g/day (21)	3.6	IPM	8
2	13 (13)	(1.1–2.0)	296.4	2 g/day (14)	8.7	NIT	7
3	11 (7)	1.9§	413.1	3 (1)	NA	AMP/GEN	4
4	6 (5)	2§	457.2	42 (3)	NA	CAZ	4
5	11 (9)	(1.2–3.8)	578.8	60 (10)	14.7	None	3
6	10 (9)	(0.5–4.8)	N/A	70 (5)	NA	CAZ	4
7	9 (9)	(0.6–16.7)	185	60 (3)	NA	None	6
8	13 (10)	(2.4–7.7)	283.3	48 (7)	6.2	NAF/RIF	3
9	23 (15)	(3.9–18.5)	467	60 (27)	(9.6–76.3)	CTX/TOB	4
10	16 (16)	(7.7–15.8)	N/A	60 (15)	6.5	None	10
11	10 (6)	(9.0–14)	272.2	60 (10)	10.7	CTX/FLG	4
12	10 (7)	22.1§	123.3	60 (16)	10.3	CTX	8
13	11 (7)	(43.8–65.8)	N/A	60 (5)	15.3	None	5
14	3 (2)	(54.8–73.8)	44	51 (14)	(4.2–54.8)	None	3
15	6 (4)	(5.6–16.7)	306	40 (5)	(10.8–12.9)	None	5
16	4 (3)	(9.9–28.4)	504	54 (7)	NA	GEN/FLG/CAZ	2
17	15 (14)	(1.0–187.3)	1054	40 (5)	NA	AMP/CTX/NAF	9

* = *mg/mL*
† = *all dose in mg/kg/d unless otherwise noted*
‡= *the first day the culture was negative on vancomycin*
§ = *patient only had one CSF vancomycin concentration drawn*

DISCUSSION

Ninety percent of organisms infecting CSF shunting devices are *Staphylococcus* and *Streptococcus species*.[17] Several series have reported that staphylococcal organisms (i.e., *S. epidermidis* or *S. aureus*) account for 50% to 60% of shunt infections, with the remainder being caused by *Streptococcus* species, *Cornebacterium* species, gram-negative bacillus, diptheroids, and micrococcus species. These numbers are consistent with the organism profile noted in our series of patients with 70.5% of infections caused by *S. epidermidis* and 17.6% caused by *S. aureus*.

Although these infections can be associated with significant morbidity and mortality, a standardized therapeutic approach has not been universally accepted. Empiric IVT vancomycin doses (i.e., 5, 10, 20 mg/day) have resulted in unpredictable CSF vancomycin trough concentrations. In our series, all patients except one received an IVT dose of 10 mg in conjunction with IV vancomycin. The 10 mg IVT dose is larger than that suggested by Gump, who advocates that the IVT vancomycin dose should not exceed 5 mg/day unless CSF concentrations are inadequate.[18] However, our doses are lower than the 20 mg/day dose in children and are equal to the 10 mg/day dose in newborns that McLaurin and colleagues recommended.[19] Based on results from a small series of patients, Pfausler et al. also recommended that a 10 mg IVT dose of vancomycin would achieve mean trough CSF vancomycin concentrations between 5–10 μg/mL in shunt-associated ventriculitis.[20]

The magnitude and range of vancomycin trough CSF concentrations following a 10 mg dose of IVT vancomycin was extremely variable in our study. Patients had resultant trough CSF vancomycin concentrations ranging from 0.4 to 187.3 μg/mL. The varibility is similar to that noted by Bayston et al. who reported that CSF vancomycin concentrations ranged from 5 to 236 μg/mL.[1] The mean maximum CSF concentration noted in our study was higher (18.4±21.8 μg/mL; range 0.4–187.3 μg/mL) than that noted by others.[19,20] Likewise, concentrations resulting from a 10 mg IVT dose were higher in infants than what was suggested by McLaurin.[19] Fifty-five percent of our infants ≤10 kg had a CSF trough vancomycin concentration >20 μg/mL. All four adolescents in our series ≥25 kg had CSF vancomycin concentrations ≤5 μg/mL. These finding are consistent with Bayston et al. who reported that larger doses (i.e., 20 mg/day) should be administered to adults based on larger ventricular size and volume.[1]

CNS volume of distribution (Vd) and clearance of vancomycin may be altered in patients with shunt infections. Normally, CSF is completely exchanged 3–4 times per day,[21] thereby influencing drug clearance from the CSF. In addition, most patients with ventriculitis whose shunts are externalized have abnormal CSF circulation. Likewise, diseases such as hydrocephalus and ventriculitis may also alter the dynamics of the CSF.[4] The majority of drug clearance occurs by bulk flow of CSF across the arachnoid villi.[22] Patients with ventriculitis may have decreased clearance of vancomycin secondary to a fall in CSF production.[23] A significant decrease in the rate of CSF formation has been reported using a rabbit model of acute ventriculitis.[24] In this model, CSF formation decreased by 48%–53% (culture-proven infection) and 56%–66% (clinical signs of infection) when compared to controls without CNS infection.

On the other hand, Haworth et al. noted that the clearance of vancomycin following a 3 mg dose was not significantly changed in rabbits with ventriculitis when compared to controls.[24] Conversely, rabbits that received a larger dose of vancomycin (120 mg) had slower elimination rates.[24] These findings imply that the CSF clearance of vancomycin may display a dose-dependent saturable characteristic. An 82-year-old male who received 50 mg IVT vancomycin was noted to have a stable Vd that reflected the physiologic CSF volume (0.25 L).[25] These authors also noted that the elimination half-life doubled after 24 hours of therapy (9.3 hours vs. 20.5 hours). Accumulation of vancomycin following IVT administration has also been reported by other investigators.[3,19,21]

Bayston et al. did not find any correlation between age and vancomycin CSF concentration.[1] Similar to Bayston et al., we did not find a significant correlation between age and CSF vancomycin trough concentrations. Based on retrospective data, Bayston and colleagues also suggested that the dose of IVT vancomycin should be based on ventricular volume.[1] They recommended that patients with ventricular size equal to or larger than those of an average adult be

given 20 mg/day of IVT vancomycin.[1] This is inconsistent with LeRoux who reported that ventricular volume did not correlate with CSF vancomycin concentrations.[26] Because our study was retrospective, we did not assess ventricular volume using MRI; however, we found no correlation between the daily output of CSF and CSF trough vancomycin concentrations

While there is no clear reference range for vancomycin in the CSF, several authors have suggested "desired concentrations" based on individual experiences and have attempted to associate this with a specific dose. Theoretically, CSF vancomycin concentration <5 μg/mL and >10 μg/mL are not warranted. This is supported by Nagal et al. who prospectively studied the bactericidal activity of vancomycin in CSF.[12] They examined the *invitro* activity of vancomycin at high concentrations against *S. aureus* and *S. epidermidis* in human CSF samples. They found equal efficacies for concentrations of 10, 100, and 300 μg/mL. A concentration of 5 μg/mL showed slightly lower activity, but this difference was not significant, whereas a concentration of 2 μg/mL was significantly less bactericidal. All patients in our study had microbiological and clinical cures. These cure rates are suprising because 35% of patients did not achieve CSF trough vancomycin concentrations >5 μg/mL. Although higher CSF vancomycin concentrations occurred over the dosing interval and may have been adequate to treat most CSF infections, it is the trough concentrations that have been monitored and associated with outcome.[12]

One patient in our study developed chronic eosinophilia in the CNS, which was assumed to be associated with an elevated CSF vancomycin concentration (187.3 mg/mL. Although other factors can contribute to CSF eosinophilia (e.g., the shunt as a foreign body), this side effect is consistent with two case reports previously described.[27] In order to reduce the potential for toxicity, Pau et al. adjusted vancomycin dosages to maintain CSF trough concentrations below 20 μg/mL.[3]

CONCLUSIONS

Although CSF trough vancomycin concentrations are highly variable following the administration of a 10 mg IVT dose of vancomycin, we recommend beginning with 10 mg/day of IVT vancomycin in conjunction with age-appropriate IV vancomycin dosing for CNS infections. The variability in CSF concentration after this dosage requires practitioners to monitor trough CSF vancomycin concentrations and calculate the pharmacokinetic parameters (e.g., volume of distribution, CSF elimination half-life) after initial dosing.[28] Our series of patients suggests that concentrations appear to be lower in older children (i.e., <5 μg/mL) and elevated in younger patients <10 kg (i.e., >20 μg/mL). This may require doses of 20 mg/day of IVT vancomycin in adolescents or in patients who are unresponsive to initial doses.[25,28] Likewise, if CSF trough concentrations are elevated in infants or in patients experiencing non-linear clearance from the CSF, doses of 5 mg/day may be indicated. Because dosing recommendations for IVT vancomycin are debatable and guidelines that reflect a CSF vancomycin dose-concentration relationship are unavailable, there is a need for well-designed prospective studies to determine the optimal therapy of IVT vancomycin that would insure success while avoiding toxicity.

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CLINICAL INVESTIGATION

Plasma Concentrations Following Application of Whole versus Cut Transdermal Clonidine Patches To Critically Ill Children

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Clonidine is used for hypertension and narcotic withdrawal prophylaxis in adults and children. This study described plasma absorption of clonidine from whole and cut transdermal clonidine patches. This was a retrospective descriptive study in an 18 bed multidisciplinary pediatric intensive care unit, evaluating 15 critically ill children with a median age of 1.1 years (range 0.3–11 years) treated with transdermal clonidine for narcotic withdrawal prophylaxis, and who had plasma clonidine concentrations measured. An assessment of the relationship between clonidine dose and patch integrity (whole vs. cut) with plasma concentrations was performed, with further analysis by Spearman Correlation Coefficient. Clonidine doses averaged 7.5±4.2 μg/kg/day (range 2.3–20 μg/kg/day) for 9.8±4.3 days (range 4–20 days). There were 9 cut patches and 6 whole patches. The average prescribed dose delivered by cut patches was 6.4±3 μg/kg/day, resulting in a mean plasma concentration of 1±1.1 ng/mL (range <0.05–3.3 ng/mL). The average prescribed dose delivered by whole patches was 7±1.7 μg/kg/day, resulting in a mean plasma concentration of 0.55±0.3 ng/mL (range 0.13–1.5 ng/mL). The Spearman Correlation Coefficient was calculated to evaluate the correlation between dose and concentration. For whole and cut patches the correlation coefficient was 0.94 (P=0.005) and 0.72 (P=0.002), respectively. Doses ranging from 1.7 to 20 μg/kg/day using whole patches resulted in no plasma concentrations >2 ng/mL. However, a plasma concentration >2 ng/mL was achieved with a dose of 8.8 μg/kg/day delivered by a cut patch. In addition, the 2 samples that resulted in undetectable concentrations were taken from patients who were treated with cut patches. The results from this pilot study suggest that critically ill children absorb clonidine from transdermal patches, but the rate and extent of absorption appears to be more predictable with the use of whole patches compared to patches that have been cut.

KEYWORDS: clonidine, patch, transdermal

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INTRODUCTION

Children who require mechanical ventilation commonly receive prolonged intravenous analgesia and sedation. The use of opiates and sedatives for more than five days often results in narcotic and benzodiazepine tolerance and dependence.[1-4] The management of withdrawal symptoms is a challenge frequently faced in the pediatric intensive care unit (PICU) setting. Few guidelines exist to treat or prevent withdrawal symptoms in pediatric patients.[5-7] A medication with minimal side effects that provides adequate prophylaxis against withdrawal is desirable in this setting.

Clonidine, widely used as an antihypertensive medication, is an alpha-2 adrenergic receptor agonist that centrally inhibits presynaptic sympathetic nervous system outflow. Clonidine's mechanism of action results in a decrease in cir-

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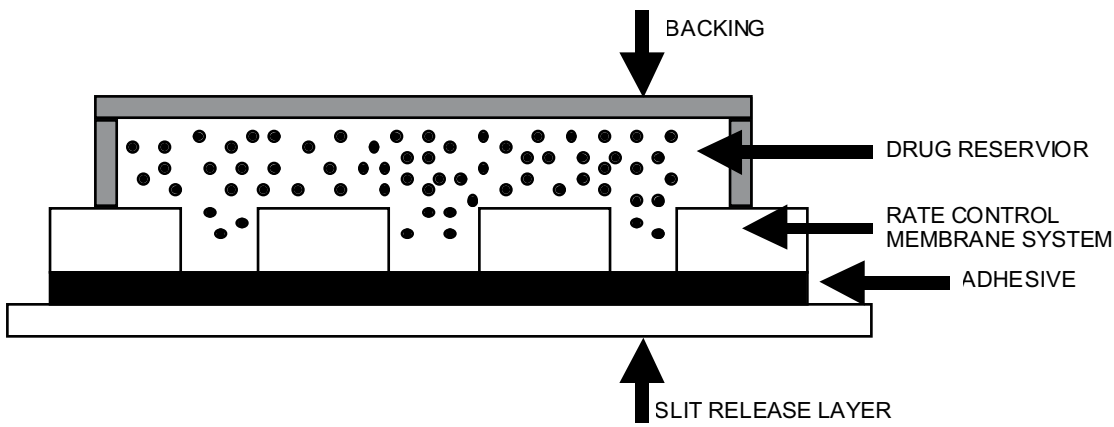
culating blood levels of epinephrine and norepinephrine. This action can prevent the symptoms of excessive catecholamine release, which occurs during opiate withdrawal.[8,9] Clonidine reduces opiate withdrawal symptoms when used in adults[8,10-13] but data is limited in critically ill children.[2,14]

Oral clonidine may reduce narcotic abstinence symptoms in neonates exposed to methadone *in utero*.[15] The utility of clonidine as a treatment for opiate withdrawal was first documented in 1978.[10] Several studies have been published since then describing its use in the management of narcotic withdrawal. These studies document oral clonidine doses of 5 μg/kg/day, and other regimens that start with 100 μg/day orally with dose increases titrated to achieve the desired clinical effect.[11,13,16-18] The use of clonidine for treatment of neonatal narcotic abstinence syndrome was well documented in 1984 using doses of 0.5 to 4 μg/kg/day.[19] A single case series suggests the utility of transdermal clonidine in the prevention of opioid withdrawal symptoms following laryngotracheal reconstruction in PICU patients.[14] However, clonidine plasma concentrations and pharmacokinetics were not assessed in this case series. Although a literature search did not reveal any studies correlating plasma concentrations with efficacy in the treatment of narcotic withdrawal, plasma concentrations >2 ng/mL resulted in an increased occurrence of side effects[20] including dry mouth, bradycardia and sedation.[13,16,17] There currently is no established reference range for plasma clonidine concentrations in the treatment of pediatric narcotic withdrawal.

Clonidine is available for use in tablet form, epidural and IV use, rectal use, and as a transdermal patch. Oral delivery is not practical for all critically ill children. Epidural administration is invasive and requires extensive monitoring. The transdermal approach is a rational route of drug administration in the PICU setting. Transdermal clonidine (Catapres-TTS, Transdermal Therapeutic System - Boehringer Ingelheim, Ridgefield CT) is a multi-layered unit that releases drug at a constant rate when applied to intact skin (Figure 1). The system includes a 4-layer laminate consisting of an occlusive protective backing that maintains proper skin hydration for drug delivery, a gelled reservoir of active drug dispersed within a highly drug-permeable matrix, a microporous membrane that controls the constant dosage rate, and an adhesive coating that attaches and primes the skin surface with drug. Prior to use, a protective slit release liner of polyester that covers the adhesive layer is removed. Following application to intact skin, the clonidine contained in the adhesive layer saturates the skin site below. Clonidine in the drug reservoir then begins to flow through the rate-controlling membrane and adhesive layer into the systemic circulation via the capillaries within the skin.[21] The amount of drug delivered is proportionate to the surface area of the patch. The 3.5, 7 and 10.5 cm^2 systems deliver 100, 200 and 300 μg/day, respectively.[22] In adults, steady state is attained within two to three days after whole patch application, and consistent clonidine concentrations are maintained without the peaks and troughs associated with conventional oral therapy.[20] In clinical practice, especially when caring for pediatric patients, doses less than 100 μg/day may be desired. If a

Figure 1. Cross sectional representation of the clonidine transdermal drug delivery system.[28]



physician prescribed a dose of 50 μg/day, half of a 3.5 cm^2 patch would be applied to the patient. At our institution, it is standard for the patches to be cut in the pharmacy. Theoretically, cutting clonidine patches in half or quarters could provide accurate dosing, but it is speculated that cutting the patch may alter the drug release properties of the dosage form. Unfortunately, there is little published data regarding the effect of cutting clonidine transdermal patches on the reliability of absorption.[23] The purpose of this pilot study was to describe the impact physically cutting clonidine transdermal patches has on systemic absorption by pediatric patients.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, the charts of 15 critically ill children treated with transdermal clonidine for narcotic withdrawal and who had a plasma clonidine concentration measured within four days of patch placement were available for review. All plasma concentrations were drawn after the placement of the first patch. Collected data included patient age, diagnosis, dose and duration of narcotic infusion, dose and duration of transdermal clonidine, patch integrity (cut or whole), and the time after patch placement when the blood was collected for plasma concentration measurement. During the time period reviewed, there were no predetermined criteria mandating the assessment of plasma clonidine concentration in these patients. However, it was common practice at this institution for clinicians to measure plasma clonidine concentrations to assess absorption or potential association with non-specific symptoms of withdrawal or toxicity.

Plasma samples were sent to SmithKline Beecham Clinical Laboratories (Willow Grove, PA) and analyzed by high performance liquid chromatography/tandem mass spectrometry. The interday and intraday coefficient of variation for the clonidine assay were 10% and the lower limit of detection was 0.05 ng/mL.

RESULTS

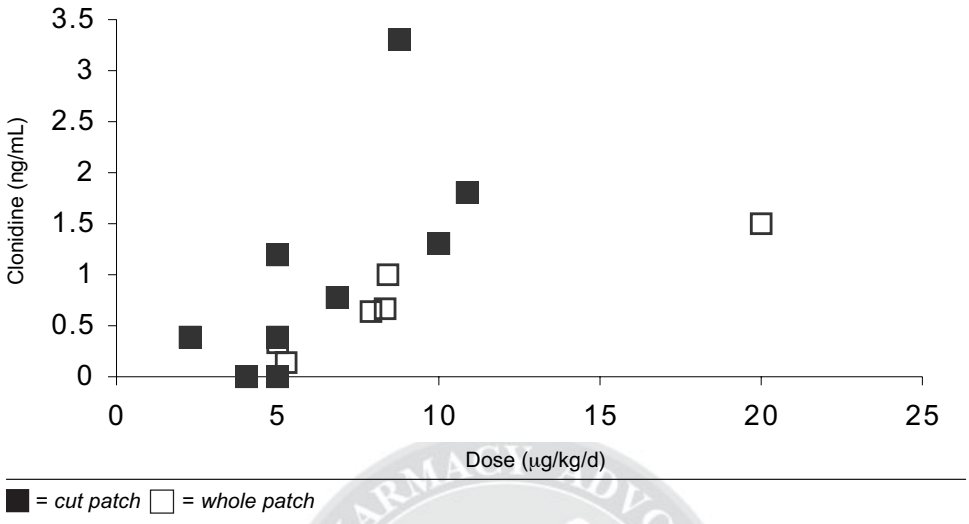
The medical records of fifteen critically ill children with a median age of 1.1 years (range 0.3–11 years) who received prolonged (>3 days) continuous morphine or fentanyl infusions and

Table: Results

Pt	Age (years)	Wt (kg)	Diganosis	Patch Integrity	Dose (mcg/kg/d)	Duration (d)	Concentration	
							Day Collected	Value
1	0.3	4.7	bronchiolitis	Cut	5	6	4	ND*
2	0.6	6.6	BPD, tracheomalacia	Cut	5	20	3	1.2
3	0.6	10.8	subglottic stenosis	Cut	4	7	4	ND
4	1.1	22	status post cricoid split pneumonia; septic shock; ARDS	Whole	20	10	3	1.5
5	4	11.8	pneumonia; toxic shock syndrome	Cut	2.3	13	3	0.4
6	2	5.7	subglottic stenosis; status post tracheal reconstruction	Whole	8.4	7	4	1
7	0.3	2.3	bronchiolitis	Cut	8.8	14	3	3.3
8	0.3	12	subglottic stenosis	Cut	10.9	7	4	1.8
9	2	10	status post cricoid split craniopharyngioma resection	Whole	8.3	7	3	0.68
10	1.4	12.6	nephrectomy; pancreatic resection	Cut	5	7	3	0.38
11	1.3	38	epilepsy requiring intubation	Whole	7.9	7	4	0.64
12	11	3	subdural abscess; sepsis syndrome	Whole	5.3	13	4	0.13
13	0.6	7.4	BPD; tracheomalacia	Cut	10	4	3	1.3
14	0.6	20	BPD, ARDS	Cut	6.8	14	4	0.79
15	6	4.7	epilpesy status post trauma	Whole	5	11	3	0.32

ARDS, acute respitatory syndrome; BPD, bronchopulmonary dysplasia; ND, not detected

Figure 2. Plasma concentration as a function of dose administered for cut (n=9) and whole (n=6) patches. Each data point represents a different patient.



subsequent treatment with transdermal clonidine were reviewed.

Results are reported in the Table. Clonidine doses averaged 7.5±4.2 μg/kg/day (range 2.3–20 μg/kg/day) for 9.8±4.3 days (range 4–20 days) for all patients. There were 9 cut patches and 6 whole patches. Clonidine plasma concentrations were drawn 3 days after patch placement for 8 patients (5 cut and 3 whole) and 4 days after patch placement for 7 patients (4 cut and 3 whole). Since plasma steady-state concentrations are achieved within two to three days after patch application, it was assumed that all measured plasma concentrations were at steady-state.

The plasma concentrations achieved as a function of dose are depicted in Figure 2. The average prescribed dose using cut patches was 6.4±3 μg/kg/day resulting in a mean plasma concentration of 1±1.1 ng/mL (range <0.05–3.3 ng/mL). The average prescribed dose using whole patches was 7±1.7 μg/kg/day resulting in a mean plasma concentration of 0.55±0.3 ng/mL (range 0.13–1.5 ng/mL). The Spearman Correlation Coefficient was calculated to evaluate the correlation between dose and concentration. For whole and cut patches the correlation coefficient (r) was 0.94 (P=0.005) and 0.72 (P=0.002), respectively. Doses ranging from 1.7 to 20 μg/kg/day using whole patches resulted in no plasma concentrations >2 ng/mL. However, a plasma concentration >2 ng/mL was achieved with a dose of 8.8 μg/kg/day delivered by a cut patch. Both samples that resulted in undetectable concentrations were taken from patients who were treated with cut patches (Table 1).

DISCUSSION

The results from this pilot study suggest that plasma clonidine concentrations resulting from placement of a cut patch are more variable than those from a whole patch. The impact of cutting transdermal patches on drug delivery is not well documented. One case report describes the use of a cut fentanyl patch in a 22-year-old male suffering from neuropathic pain in his right leg. One-fourth of a fentanyl patch (50 mcg/hour) was applied. Sixty minutes after applying one-fourth of a fentanyl patch (50 mcg/hour) the patient developed signs of opioid intoxication The patient recovered after the patch was removed.[24]

There currently is no established reference range for plasma clonidine concentrations in the treatment of pediatric hypertension or narcotic withdrawal. In adults, the antihypertensive effects correlate with plasma concentrations between 0.2 and 2 ng/mL and are dose-dependent.[20] The pharmacokinetics of clonidine have been described in adults and children. In adults, the peak plasma concentration was 1 ng/mL approximately 2 hours after an oral 300 μg dose. The elimination half-life was 8 to 14 hours.[20] Following a single intravenous dose in children, the half-life was 5.5 hours and volume of distribu-

tion was 0.96 L/kg.[25] Rectal administration of 2.5 μg/kg in children achieved an average maximal concentration of 0.77 ng/mL in approximately 52 minutes, with a terminal half-life of 12.5 hours.[26]

The pharmacokinetics of transdermal clonidine have been described in adults but not in critically ill infants and children. In adults, the intact transdermal system results in plasma clonidine concentrations comparable to those achieved with oral administration, without large fluctuations in plasma concentrations.[20] After the application of increasing sizes of transdermal clonidine systems (0.1, 0.2, and 0.3 mg) to the upper outer arm of six adult subjects, the mean steady-state plasma concentrations were 0.39, 0.84, and 1.12 ng/mL, respectively. Plasma concentrations within the reference range were achieved by two to three days after patch placement. The half-life ranged from 14 to 16 hours. No significant decline in plasma concentrations was noted until the tenth day of wear. In addition, there were no significant increases or decreases of plasma concentrations following patch change.[27]

This study was limited by a retrospective design that included a small sample of patients, lack of standardization of anatomic location of patch placement, lack of predetermined criteria for obtaining a plasma clonidine concentration, and a lack of consistent timing of samples after patch placement. This study included patients with a wide age range, introducing variability in terms of age-related clearance of clonidine. In addition, since the study was performed retrospectively, cutting of the patches was not standardized. There are no institutional guidelines that direct dosing, cutting or placement of the patch. Drug interactions and organ system failures that may have impacted on plasma concentrations in these critically ill patients cannot be excluded. Since data on withdrawal symptoms was inconsistently available, the therapeutic range for narcotic withdrawal treatment cannot be estimated. Serial pharmacokinetic sampling on individual patients is necessary to better describe the relationship between plasma concentration and the ability to manage narcotic withdrawal, and should include the measurement of catecholamine concentrations.

CONCLUSION

Critically ill children absorb clonidine from transdermal patches, but the rate and extent of absorption appears to be more predictable with the use of whole patches compared to patches that have been cut. A larger, prospective study is warranted to determine the pharmacokinetic profile, safety and efficacy of transdermal clonidine for the management of narcotic withdrawal prophylaxis in critically ill children.

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CASE REPORT

Methemoglobinemia Associated with Metoclopramide Therapy in a Neonate

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With the removal of cisapride from the U.S. market, practitioners have increasingly used other medications, such as metoclopramide, to treat gastroesophageal reflux in pediatric patients. We describe the case of a neonate who developed methemoglobinemia after receiving metoclopramide at doses slightly above the recommended age-appropriate dosage. Health care providers should be aware of this potentially serious side effect in young infants who receive this medication.

KEYWORDS: methemoglobinemia, metoclopramide, neonate

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INTRODUCTION

Cisapride (Prepulsid, Janssen Pharmaceutica, Titusville, NJ) was removed from the U.S. market in July of 2000 following continuing reports of heart rhythm disorders and deaths. Although it is still available for patients with unusual, debilitating problems for whom there is no alternative therapy, the majority of pediatric patients must use alternative medications for the treatment of gastroesophageal reflux disease. One such drug that is frequently being prescribed is metoclopramide (Reglan, Wyeth Pharmaceuticals, Collegeville, PA). Like many medications used in the pediatric arena, metoclopramide is not approved by the Food and Drug Administration for use in those <18 years of age. Although pharmacokinetic and pharmacodynamic studies of metoclopramide have been performed in the pediatric population,[1] particularly in neonates,[2,3] the available information is limited. Therefore, neonates may be at increased risk for the development of adverse effects associated with metoclopramide, including lethargy, irritability, diarrhea, extrapyramidal symptoms, and seizures.[2-4]

An increased risk of methemoglobinemia in metoclopramide-exposed infants has been reported.[5-7] Case reports have been limited to patients receiving large doses, to those given the parenteral formulations of the drug, or to patients with concomitant diarrheal illness.[5-7] We describe the case of a neonate who developed methemoglobinemia after receiving metoclopramide at 0.33 mg/kg/dose orally every 6 hours.

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CASE REPORT

A 10-day-old 3 kg neonate was seen by her pediatrician for the complaint of excessive crying for 5–10 minutes after breastfeeding. Feeds were not associated with emesis. The pregnancy history was remarkable for two previous maternal spontaneous abortions and vaginal bleeding during the first trimester with this pregnancy. The full-term newborn was delivered at a birth weight of 2.98 kg by spontaneous vaginal delivery. No problems were noted after birth, and the infant was discharged home at two days of age. The social history was significant for tobacco exposure in the home, and the family history was negative.

Based on the above history, the 11-day-old was prescribed ranitidine 15 mg by mouth twice daily (10 mg/kg/day) and metoclopramide 0.6 mg by mouth every 6 hours (0.2 mg/kg/dose) for presumed esophagitis with gastroesophageal reflux. One day after beginning the medication, the mother noticed that the baby appeared "dusky" despite feeding well. She also had

several loose stools but did not have an increased frequency of stools. The mother noted that the baby had a brief period of apnea during a feed; however, the apnea responded to stimulation. The baby continued to breastfeed well for a minimum of 30 minutes every three hours. Over the following 24 hours, the mother and grandmother noted a worsening "dusky" color and an increasing frequency of apneic episodes; these episodes were of several seconds duration and occurred 2 to 3 times. The apnea responded to stimulation and at times was associated with emesis.

At 13 days of age, the infant was evaluated in the emergency department of the referring hospital where she was noted to have blue-grey discoloration of the skin and lips. She also had 5 to 6 episodes of brief "apnea" of 5 to 10 seconds each, but an otherwise normal physical examination. The respiratory rate was 35 breaths per minute, and the SpO_2 on room air was 90%. An arterial blood gas was pH 7.51, pCO_2 23, pO_2 141, HCO_3 18 and the calculated saturation was 99%. She was placed on nasal cannula oxygen and transported to Arkansas Children's Hospital.

On admission, the history was also notable for mother's report that the infant had been receiving ranitidine 15 mg twice daily. Instead of receiving the prescribed 0.6 mg every 6 hours of metoclopramide, the newborn had been given 1 mg every 6 hours (0.33 mg/kg/dose). Due to an error in administration, the baby had received a larger-than-prescribed dose of metoclopramide since starting the medication for a total of 10 doses. The physical examination revealed a 3 kg baby (20 grams above the birth weight) who was alert, fussy but consolable, with a'"dusky" grey color on nasal cannula oxygen. The vital signs were as follows: temperature 36.5 °C, pulse 136 beats per minute, respiratory rate 28 breaths per minute, and blood pressure 103/72 mm Hg. The oxygen saturation by pulse oximetry was 91% on 1.5 L/min of oxygen by nasal cannula (100% FiO_2). The remainder of the physical examination was normal. The infant had normal skin turgor, moist mucous membranes, and no respiratory distress.

The laboratory evaluation included cultures of blood, urine, and spinal fluid. Electrolytes and complete blood count were normal. There was a discrepancy between the calculated saturation by the arterial blood gas (99%) and the oxygen saturation by pulse oximetry (90%) from the referral hospital. The patient also continued to be cyanotic despite a normal PaO_2, hence, an arterial blood gas with co-oximetry and methemoglobin level was obtained: pH 7.43, pCO_2 29, pO_2 140, HCO_3 19, and base excess –2.9. The initial methemoglobin level was 16%, and measured oxygen saturation was 52.6%.

Metoclopramide and ranitidine were discontinued. The infant was treated empirically with ampicillin and cefuroxime for potential infection. Approximately four hours after admission, the patient had a brief apneic episode that responded to gentle stimulation. Five hours later, she had prolonged apnea (>20 sec), which responded to positive pressure ventilation. A repeat methemoglobin level at this time was 27.5%. She received 5 mg of methylene blue (1.67 mg/kg) intravenously over 5 minutes. The methemoglobin level one hour later was 1.1%. She had no apnea for the subsequent 24 hours, but apneic events recurred and were associated with oxygen desaturation by pulse oximetry. A repeat methemoglobin level at this time was again 1.1%. The patient was transferred to the Pediatric Intensive Care Unit for observation.

Further evaluation the following day included an electroencephalogram and a head ultrasound, which were both normal. An upper GI was significant for reflux to the thoracic inlet. A simultaneous sleep evaluation (including thermistry, chest wall impedance, SpO_2, and heart rate recordings) and pH probe were completed on the fifth day of hospitalization. The pH probe revealed increased frequency as well as prolonged duration of reflux episodes. The sleep evaluation revealed excessive episodes of periodic breathing, which did not correlate with the reflux episodes. The blood, urine, and spinal fluid cultures were negative at 72 hours, and antibiotics were discontinued. The hemoglobin electrophoresis was normal.

Therapy for gastroesophageal reflux was initiated with oral ranitidine (2 mg/kg/dose twice daily) and bethanechol (0.2 mg/kg/dose three times daily). Oxygen was weaned to 1/8 lpm (100% FiO_2) with feeding and sleeping only. On this regimen, the patient had no further apneic events for 48 hours and was discharged home on oxygen, an apnea monitor, and a pulse oximeter. The patient's primary care physician weaned the oxygen over the next few weeks. No further episodes of cyanosis were reported.

DISCUSSION

Methemoglobinemia has been described as an adverse effect of metoclopramide.[7,8] A limited number of case reports have addressed the occurrence of methemoglobinemia in infants exposed to metoclopramide.[5-7] Due to the increased frequency of metoclopramide use in recent years, it is important for health care providers to be aware of this potential adverse effect. The patient described here presented with clinical cyanosis and apnea in the absence of respiratory distress. The cyanosis resolved after treatment with methylene blue and discontinuation of metoclopramide. Although diarrheal illness with acidosis has been associated with methemoglobinemia in infants,[9,10] the neonate in the current report did not experience significant diarrhea or acidosis.

Methemoglobin is formed when the hemoglobin molecule is oxidized from the normal ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. In normal individuals, the level of methemoglobin is maintained at less than 0.6% by cytochrome b_5 reductase (NADH-dependent methemoglobin reductase).[10] If low levels of this enzyme are present, or if the red blood cells are under excessive oxidative stress, methemoglobin levels may rise.[10, 11-12] Metoclopramide or its metabolites have been postulated to have a direct oxidizing effect on erythrocytes.

Neonatal methemoglobinemia may be congenital or acquired. Congenital methemoglobinemia is due either to a defect in the cytochrome b5 reductase system (autosomal recessive form) or to inheritance of one of the M hemoglobins that binds ferric iron preferentially (autosomal dominant form).[10] Our patient's hemoglobin electrophoresis was normal, thus eliminating abnormal hemoglobin (hemoglobin M) as a potential cause of the methemoglobinemia. After discharge, a NADH-methemoglobin reductase level was to be obtained by the primary care physician, but the infant was lost to follow-up.

The acquired form of methemoglobinemia may be due to exposure to agents such nitrate-contaminated water,[12] nitrate-contaminated foods (e.g. vegetables),[13,14] inhaled nitric oxide,[15] metoclopramide,[5,6] topical anesthetics (benzocaine, prilocaine, and lidocaine/prilocaine cream (EMLA),[16] and other medications or environmental exposures.[16] The infant did not have exposure to other drugs associated with methemoglobinemia.[11] Transient methemoglobinemia associated with acute diarrheal illness and acidosis has also been reported, although the mechanism for this association is not clear.[9]

Metoclopramide, a derivative of orthoprocainamide, is primarily metabolized (at the first pass through the gut wall or liver) to metoclopramide N-4-sulfate, but as much as 25–40% of the parent compound may undergo renal clearance.[17] In addition, CYP2D6 may also be involved in the metabolism of metoclopramide.[18] In neonates, developmentally determined changes in hepatic metabolism and renal clearance may significantly alter the pharmacokinetics of metoclopramide, thereby increasing the risk of side effects.

Two pharmacokinetic studies have been performed in infants, with a total of 16 infants included.[2,3] The first study included 6 full-term infants (0.9–5.4 months).[2] One dose of metoclopramide in this populationcleared at a mean of 0.66 L/hr/kg (range: 0.15 to 1.29 L/hr/kg). The youngest subject was 3.5 weeks of age. Based on a first-dose pharmacokinetics study, this infant had a markedly prolonged elimination half-life (23.1 hours), which decreased to 10.3 hours at steady state. A wide variation in the clearance of a single dose of oral metoclopramide was reported (Cl=0.15 to 2.43 L/hr/kg) in a follow-up study involving premature infants with a mean gestational age of 31.2±3.2 weeks.[3] Three of ten infants had elimination half-lives in excess of 10 hours.[3]

Previously reported values for the clearance of metoclopramide in adults were 0.53±0.19 L/hr/kg[19] and 0.55±0.12 L/hr/kg.[20] In a pharmacokinetic study of 9 older children (7–14 years of age) receiving metoclopramide for cytotoxic drug induced vomiting, clearance values appeared to be more comparable to adults with less variability than that reported in infants (0.56±0.1 L/kg/hr).[21] In addition, normal pharmacogenetic variability in sulfotransferase isoforms and CYP2D6 may also contribute to variability in metabolism between individuals.[2,22]

Two other mechanisms may account for the increased rate of methemoglobinemia in young infants exposed to metoclopramide. First, the erythrocyte activity of cytochrome b_5 reductase, which is responsible for reducing methemoglobin, is age-dependent; therefore, newborns and

premature infants may have transient enzymatic deficiency resulting in lower enzyme levels.[10,23] Secondly, neonates have increased levels of fetal hemoglobin, which may be more readily oxidized than the adult form.[10]

Previous reports of methemoglobinemia in infants associated with metoclopramide have primarily included infants who were receiving larger doses of metoclopramide or were receiving the drug by the parenteral route. For example, one case report described an 18-day-old who developed methemoglobinemia after receiving metoclopramide 0.7 mg/kg/day intravenously (including 0.2 mg/kg every 4 hours for three doses).[6] This patient became dusky and was noted to have a dark arterial blood sample despite a high pO2. The methemoglobin level was 23.2%. He fully recovered after discontinuation of metoclopramide. Methemoglobinemia has also been reported in a 3-week-old infant who received metoclopramide 1 mg/kg/dose orally every 6 hours over a 36-hour period for gastroesophageal reflux. He became cyanotic, lethargic, irritable, with poor feeding, diarrhea and respiratory distress. The methemoglobin level in this newborn was 20.5%. The methemoglobinemia and associated symptoms resolved quickly after one dose of methylene blue.[5] Both of these patients had normal methemoglobin reductase levels and no measurable hemoglobin M.

The recommended dose for metoclopramide is 0.4–0.8 mg/kg/day in four divided doses.[11,24] The present case represents a very young neonate who received a metoclopramide dose slightly above what is age-appropriate for the recommended dose. The etiology of this patient's apnea is unknown. The apneic spells persisted greater than 24 hours after resolution of the methemoglobinemia but resolved prior to hospital discharge. Respiratory depression has been described in the continuum of symptoms associated with methemoglobinemia. In this case, the sleep study showed no association between the apneic episodes and gastroesophageal reflux.

Clinical symptoms associated with methemoglobinemia are influenced by the concentration of methemoglobin. Although cyanosis is generally present at methomoglobinen levels above 15%, they may occur at lower levels in infants.[13] At concentrations of 30 to 40%, symptoms are usually generalized (e.g., poor feeding, lethargy, and irritability). Levels greater than 55% are usually associated with more severe symptoms such as respiratory depression, cardiac arrhythmias, seizures, coma, and death. It is possible that infants may have respiratory depression and apnea at lower methemoglobin levels than are typically described for older patients.

For patients who have drug-induced methemoglobinemia, the first treatment is the removal of the causative agent. Methylene blue may be used, particularly if the methemoglobin levels are markedly elevated or if there are signs of hypoxia. The dose is 1–2 mg/kg of a 1% solution, delivered by slow intravenous infusion, and may be repeated if needed. Methylene blue is an effective electron acceptor from NADPH-dependent methemoglobin reductase and is converted to leucomethylene blue, which then reduces methemoglobin to hemoglobin. Methylene blue is contraindicated in patients with G6PD deficiency because it is ineffective and may cause a severe hemolytic anemia.[25]

G6PD deficiency is an X-linked disorder that affects primarily males, but also homozygous females. Clinically, these patients develop hemolysis after receiving oxidizing substances, including a long list of medications (e.g., fava beans, acetaminophen, methylene blue). Certain ethnic groups have a high incidence of the disease, including Italians, Greeks, and other persons of Mediterranean, Middle Eastern, African, and Asian descent.[26] Our Caucasian female patient was not tested prior to treatment with methylene blue, but was unlikely to have this disease since she had an excellent response to the drug. With the removal of cisapride from the market and the subsequent increased use of metoclopramide, particularly in the intensive care nursery, an increased incidence of methemoglobinemia and other metoclopramide-associated side effects can be anticipated.

Despite its common use in infants, metoclopramide is one of the many drugs prescribed for children with minimal pediatric pharmacokinetic/pharmacodynamic data available. Methemoglobinemia should be suspected in infants with clinical cyanosis and discordance between the calculated oxygen saturation (based on PaO_2) and SpO_2. A measured methemoglobin concentration by co-oximetry is diagnostic. Based on the available pharmacokinetic data, a starting dose of metoclopramide of 0.1 mg/kg/dose four times daily is recommended in young

infants. Larger doses may be used in a step-wise approach in infants who do not respond to lower doses. Use of dosing syringes and parent education about drug dispensing are needed to minimize dosing errors and subsequent morbidity.

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CASE REPORT

Intraventricular Tobramycin in a Premature Infant with Pseudomonas Meningitis

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A 38-week postconceptional age (29-week gestational age) infant required the placement of an Ommaya reservoir following a grade IV intraventricular hemorrhage and progressive hydrocephalus. At 70 days of age, a cerebrospinal fluid (CSF) culture was positive for *Pseudomonas aeruginosa* and the infant was empirically treated with age-appropriate parenteral doses of ceftazidime and gentamicin. This antibiotic regimen was changed to meropenem and tobramycin following the results of sensitivity reports. The infection failed to respond despite aggressive systemic dosing of antibiotics and removal of the Ommaya reservoir. Intraventricular injections of tobramycin were added to the systemic antibiotic regimen at a dose of 2 mg daily with subsequent doses adjusted to maintain trough concentrations in the CSF of 20–30 μg/mL. The CSF was sterilized after three days of intraventricular injections. The infant completed seven days of intraventricular tobramycin plus a 24-day regimen of systemic antibiotics. No acute complications were noted with the addition of intraventricular injections.

KEYWORDS: intraventricular, meningitis, neonate, tobramycin

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INTRODUCTION

Gram-negative meningitis is associated with a high rate of morbidity and mortality in neonates and requires aggressive management with systemic antibiotic therapy. Reasons for high mortality rates can be attributed to poor antibiotic penetration into the central nervous system (CNS) and antimicrobial resistance associated with bacterial meningitis. Although an inflamed meninges enhances a moieties penetration into the CNS, CSF concentrations of tobramycin following systemic administration may be insufficient to produce a bactericidal effect, particularly in an environment deficient in opsonins and complement.[1,2] In such situations, instillation of an antibiotic directly into the CNS via intraventricular (IVT) or intrathecal (IT) administration may be necessary to achieve adequate concentrations in the CNS.[1] Vancomycin, gentamicin, tobramycin, amikacin, and amphotericin B are antimicrobials that have been administered via these routes.[1] Previous IVT administration of penicillins and cephalosporins have resulted in neurotoxicities (e.g., seizures, paraplegia) that have hindered their use.[1] Mortality from *Ps aeruginosa* sepsis or meningitis has also been reported to be inversely related to postnatal age at diagnosis.[3] This report describes a premature infant with hydrocephalus who developed pseudomonas meningitis that was successfully eradicated with the aid of IVT tobramycin.

CASE REPORT

A 38-week postconceptional age (29-week gestational age) neonate was born to a 30-year-old G_4P_3 by spontaneous vaginal delivery due to preterm labor and premature rupture of the membranes. He was admitted to the intensive care nursery for respiratory distress syndrome,

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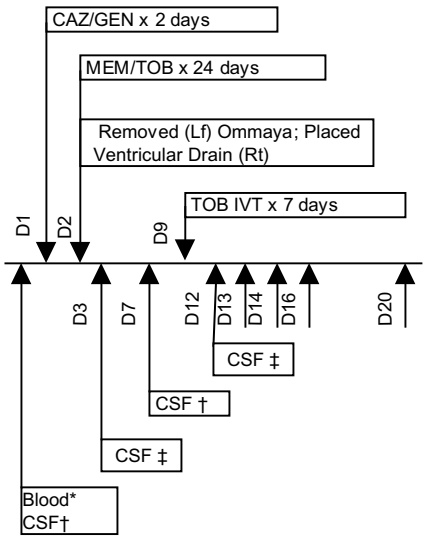
Figure 1. Antibiotic and Culture Timeline



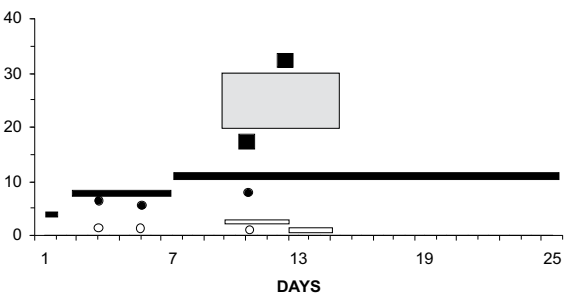
CAZ, Ceftazidime; GEN, Gentamicin; MEM, Meropenem; TOB, Tobramycin
** Blood cultures negative for pseudomonas*
† CSF cultures positive for pseudomonas: (S: Amikacin <16 mg/mL; Ciprofloxacin <1 mg/mL; Imipenem <4 mg/mL; Tobramycin <4 mg/mL; I: Gentamicin=8 mg/mL; R: Aztreonam >16 mg/mL, Ceftazidime >16 mg/mL; Piperacillin/tazobactam >64 mg/mL)
‡ CSF cultures negative

suspected sepsis, and VATER association. His initial APGAR scores were 4, 6, and 9 at 1, 5, and 10 minutes, respectively. The newborn was intubated, placed on a ventilator, and given age-appropriate doses of ampicillin and gentamicin as empiric therapy for 14 days. The patient required a thoracotomy with ligation of the tracheoesophageal fistula and G-tube placement on the third day of life. At 6 days of age, the initial neurosonogram showed the patient had developed a right-sided grade IV and left-sided grade III intraventricular hemorrhage (IVH). A repeat neurosonogram 14 days later showed dilated ventricles and bilateral grade IV IVH with progressive hydrocephalus, which required repeated CSF removal and the placement of an Ommaya reservoir on the 25th day of life.

During his first two months in the intensive care nursery, the infant was treated with numerous courses of ampicillin, gentamicin, tobramycin, cefotaxime, ceftazidime, and vancomycin for various infections. A CSF culture grew *P aeruginosa,* and empiric treatment with ceftazidime and gentamicin was initiated on day 70 of life (Figure 1, Day 1). In response to a sensitivity report indicating a highly resistant organism, the systemic antibiotic regimen was changed from ceftazidime (50 mg/kg every 8 hours) and gentamicin (4 mg/kg every 24 hours) to meropenem (40 mg/kg every 8 hours) and tobramycin (4 mg/kg every 24 hours) (Figure 1). The following day the tobramycin dosage was changed to 4 mg/kg every 12 hours and the Ommaya reservoir was removed. Despite aggressive dosing with antibiotics and removal of the Ommaya reservoir, the CSF cultures continued to grow *P aeruginosa.* The tobramycin dosage was again increased to 5.5 mg/kg every 12 hours, and IVT preservative-free tobramycin was initiated at 2mg daily.

Systemic and IVT dosing of tobramycin as well as CSF and serum tobramycin concentrations are in Figure 2. Intraventricular and tobramycin dosing was adjusted to maintain the CSF trough concentrations between 20–30 μg/mL. Doses were administered immediately after CSF sampling. Trough concentrations achieved in the CSF ranged from 17.5 to 32.4 μg/mL. Four days after beginning IVT tobramycin, CSF cultures indicated that the fluid was sterilized. Repeat CSF cultures remained negative. The patient received 24 days of systemic antibiotics in conjunction with seven days of IVT tobramycin. No acute complications were observed with the IVT injections. Despite eradication of the organism from the CSF, the patient died from cardiorespiratory failure at 118 days of age.

Figure 2. Systemic and IVT Tobramycin Dosing Accompanied by Serum and CSF Concentrations



Systemic dosing of tobramycin (mg/kg/d); ● Tobramycin peak serum concentration (μg/mL); ○ Tobramycin trough serum concentration (μg/mL); ▭ IVT dosing of tobramycin (mg/day); ■ CSF concentration of tobramycin; □ Reference range for CSF tobramycin concentration

DISCUSSION

Although systemic antibiotics failed to treat pseudomonas meningitis in this premature infant with severe hydrocephalus, concurrently administered IVT tobramycin was effective. The presence of a highly resistant organism was likely a result of exposure to numerous antimicrobial courses throughout his neonatal life. The use of IVT aminoglycosides in the management of resistant meningitis is controversial. Despite the successful eradication of the organism in this case with the regimen employed, there are many questions regarding the appropriate indications and dosing of IVT aminoglycosides.

Tables 1 and 2 review those published case reports and studies regarding the use of IVT or IT aminoglycoside antibiotics in pediatric patients. Our initial dose of 2 mg was selected using previously published case reports[4-9] and studies.[10-16] Doses of IVT tobramycin ranging from 1.5–2 mg were used in our patient to achieve CSF concentrations of 20–30 μg/mL. The initial dose of 2 mg was selected using previously published case reports[4-9] and studies.[10-16] Similar to earlier reports,[8,11,14,16] we employed a CSF goal concentration of 20–30 μg/mL in order to achieve tobramycin concentrations that were at least five times the minimal inhibitory concentration (MIC) of the organism in the CSF (<4 μg/mL). Traditionally, aminoglycosides are dosed by targeting a serum peak-to-MIC ratio of 5:10. Whether or not a similar approach should be used to "target" antibiotic CSF concentrations (i.e., peak concentration:MIC ratio) remains controversial. High antimicrobial concentrations in the CSF are required to achieve bactericidal effects due to the relative lack of local immune system function.[1,2]

Table 1. Case Reports of Previous Experience with IVT/IT Aminoglycoside Antibiotics in the Pediatric Population

References	Demographics	Antibiotic Therapy	CSF Concentration (μg/mL)	Outcome
Newman 1967[4]	3 infants; ventriculitis, (n=2), meningitis (n=1); *P pyocyanea* *K aerogenes*	GEN 1–2 mg/kg/d IM x 12–16 d *plus* GEN 0.1–2 mg IVT daily x 5–12 d	During IVT therapy <0.1–7	All cured
Moellering 1972[5]	16 mo; meningitis; *Proteus morganii*	GEN 29 mg IM q 8 hr x 11 d *plus* GEN 1mg IT qd x 4		CSF (+)
		2nd regimen: GEN 11mg IM q 8 hr x 5 d *plus* GEN 1–2 mg IT qd x 4 d	3 hr after 2mg dose=1.2	CSF (+)
		3 rd regimen: GEN 11 mg IM q 8 hr x 5 d *plus* GEN 2 mg IVT qd x 5 d	6 hr later=0.2 21–30 hr=2.4–10	CSF (-) within 24 hours after IVT initiated; Cured
Olsen 1977[6]	8 mo; ventriculitis; *P aeruginosa*	GEN 3 mg/kg/day IM x 12 d *plus* GEN 1 mg IVT qd x 12 d		CSF positive
		2nd regimen: GEN 5 mg/kg/day IM x 23 d *plus* GEN 3 mg IVT qd x 23 d	24 hr=25–35, single peak of 76	Cured
Pickering 1978[7]	6 mo; ventriculitis; *P aeruginosa*	GEN IV x 25 d (Unknown dose) GEN 2 mg IVT q 24–36 hr x 19 d	1 hr=15; 24 hr=1–5	Cured
		GEN IV x 14–17 d (Unknown dose)	1 hr=>20; 36 hr=8–14	All Cured
	3 infants: 1, 2, and 3 mo; ventriculitis; *Staphylococcus* sp.	MET IV x 3–5 d (Unknown dose) GEN 1 mg IVT q 24–48 hr x 10–19 d		
Katz 1980[8]	4 mo; VPshunt infection; *Enterobacter doacae*	GEN 2, 4, 6 mg IVT qd x 14 d *plus* CAR 400mg/kg/d IV x 21d	2 mg=1.7* 4 mg=0.7* 6 mg=19.6*	Cured
Masvosva 2003[9]	4mo; ventriculitis VP shunt; *P aeruginosa*	TOB 2.5mg/kg q 8 hr x 23 d TOB 5mg IVT qd x 21 d (intermittent) CAZ 50mg/kg q 8 hr x 38 d	During IVT therapy 1–130.8	Cured

* *trough concentration*

IVT, intraventricular; IT, intrathecal; IM, intramuscular; IV, intravenous; CAZ, ceftazidime; CAR, carbenicillin; GEN, gentamicin; TOB, tobramycin

Olsen and colleagues advocated the need for 24-hour post-dose CSF concentrations of at least 25–35 μg/mL for *P aeruginosa* ventriculitis.[6] The use of high trough concentrations in the CSF was also supported by Lorber et al.[10] This group reported a correlation between successful treatment and a trough (i.e., 24-hour post-IVT dose) gentamicin CSF concentration that 'exceeded manyfold the MIC' of the organism. Pickering and colleagues targeted a goal CSF trough gentamicin concentration that was four times the minimal bactericidal concentration (MBC) of the organism.[7] Unlike the MBC of 3.12 μg/mL reported by Pickering et al. the gentamicin MIC of the or-

Table 2. Studies of Previous Experience with IVT/IT Aminoglycoside Antibiotics in the Pediatric Population

Reference	Demographics	Antibiotic Therapy	CSF Concentrations (μg/mL)	Outcome
Lorber 1970[10]	14 infants; ventriculitis; *E coli, Proteus* sp. *P pyocyaneus*	GEN 0.5–8 mg/kg/d IM (Max 22 d) *plus* GEN 0.5–8 mg IVT qd (Max 11 d)	24 hr=0.5–80	7 cured; 7 died
Kaiser 1975[11]	6 pts, ventriculitis; *E coli*, *Klebsiella* sp. *Pseudomonas stutzeri*	TOB/GEN 5–10 mg IVT d x 10 d *plus* TOB/GEN 3–4.5 mg/kg IV qd	Within 1st 6 hrs=12.8–40 24 hrs=4–6	All cured; 1 relapse x3
Yeung 1976[12]	16 infants; 1–27*; meningitis; *E. coli*, *Pseudomonas*, *Klebsiella, Flavobacteriu, Bacillus subtilis, S aureus*	Term: GEN 4 mg IT/IVT qd x at least 7 d LBW: GEN 2mg IT/IVT qd x at least 7 d All: GEN 8 mg/kg IM qd *plus* AMP 200–400mg/kg IV qd at least 3 wks or 1 wk after IT/IVT therapy D/C	No levels	All cured; 1 had hearing loss at 5th week that returned to normal
McCracken 1976[13]	52 infants; <2yr; meningitis; gram- negative enteric	AMP 50 mg/kg IV q12 hr (≤7*) or 70 mg/kg IV q 8 hr (>7*) and GEN 2.5 mg/kg IM q12 hr (≤7*)/q8 hr (>7*) ± GEN 1 mg IT qd x at least 3 d	2–4 hr=18.4≥40 18–24 hr=0.5-3.4	No benefit of IT/IVT over systemic therapy
Wald 1980[14]	8 pts; 1mo–19yr; shunt infection or ventriculitis; *E coli*, *Enterococcus* sp. *Klebsiella* sp. *Staphylococcus* sp.	GEN 3–55 mg IV q 8 hr *plus* GEN 1–6 mg IVT qd x 4–16 d	24 hr=5.3–12.6 48 hr=1.74–13.6	7 cured; 1 relapse then cured
McCracken 1980[15]	52 infants; meningitis and ventriculitis, 28 pt; ventriculitis: 9 pt w/o ventriculitis: *E coli*, *Klebsiella* sp. *Enterobacter* sp. *Citrobacter* sp. *Salmonella* sp.	All: GEN 2.5 mg/kg IM q12 hr (≤7*) q 8 hr (>7*) plus AMP 50 mg/kg IV q12 hr (≤7*) or 70 mg/kg IV q 8 hr (>7*) GEN 2.5 mg IVT qd x at least 3 d GEN 2.5 mg IT qd x at least 3 d	1–6 hr: IVT=10–130; IT: 8–85 16–24 hr: IVT=1–24; IT=1.8-2.4	Higher mortality with IVT in meningitis group study stopped
Wright 1981[16]	8 infants; 1–10 wks; ventriculitis: *E. coli, C diversus P morganii P aeruginosa Streptococcus faecalis*	Previous therapy: Varied (IV or oral) or no antibiotics; addition of AMK 5 mg IVT qd to all patients	2–4 hr >100	6 cured; 2 died

** Days of life; AMK,amikicin; AMP, ampicillin; GEN, gentamicin; IM, intramuscular; IV, intravenous; IVT, intraventricular; IT, intrathecal; LBW, low birth weight; TOB, tobramycin*

ganism in our patient was considerably higher at 8 μg/mL.[7] Although aminoglycoside antibiotics exhibit concentration-dependent killing, numerous reports of successful clinical cure have occurred by targeting high 24-hour post-IVT dose CSF concentrations.[6,10,14,16]

CSF antibiotic concentrations and dosing requirements have been shown to vary based upon patient disease characteristics (e.g., hydrocephalus), type, and severity of infection.[4-15] Olsen and colleagues described a 6-month-old infant with hydrocephalus and a ventriculoperitoneal (VP) shunt who developed *P aeruginosa* ventriculitis.[6] Monotherapy with intramuscular (IM) and IVT gentamicin was initiated at a daily dose of 3 mg/kg and 1 mg, respectively. After 12 days of therapy, the CSF cultures remained positive, and gentamicin was increased to 5 mg/kg IM and 3 mg IVT daily. Sterile CSF cultures were achieved, and the infant received gentamicin for a total of 35 days. CSF concentrations 24 hours post dose (3 mg) ranged from 25–35 μg/mL with a single peak value of 76 μg/mL. The infant showed no signs of toxicity or reinfection at a one-year follow-up.

Another case report described a 4-month-old female with a VP shunt infection due to–*Enterobacter cloacae*. The organism was effectively eradicated by IVT gentamicin and intravenous carbenicillin.[8] Gentamicin was initiated at a dose of 2 mg/day IVT. During therapy, the daily IVT dose was increased to 6 mg in order to achieve the goal CSF trough concentration that was 30–50 times the MIC of the organism. Gentamicin CSF trough concentrations ranged from 1.7–19.6 μg/mL and no toxicities were reported during therapy. The authors concluded that patients with patent VP shunts may require two to three times the usual IVT gentamicin dose of 0.5–2 mg, and those with enlarged ventricles may need four to five times the normal dose. The purpose of their report, however, was to document successful IVT therapy and not to provide specific dosing recommendations for patients with VP shunts.

Masvosva and colleagues describe a 4-month-old infant with ventriculitis (post-VP shunt repair) who was treated with IVT tobramycin (5-mg dose), IV tobramycin, and ceftazidime for *P aeruginosa*.[9] Goal CSF concentrations were troughs between 5–10 μg/mL, and actual tobramycin concentrations in the CSF ranged from 1–130.8 μg/mL. The patient was cured; however, it was noted that four seizure episodes occurred during therapy. These events may also have been due to a concomitant brain abscess or shunt placement.

Kaiser and McGee reported six episodes of ventriculitis that were cured with the combined use of IVT and systemic administration of tobramycin or gentamicin.[11] Infections were caused by *Escherichia coli* (n=2), *Klebsiella* species (n=3), and *Pseudomonas stutzeri* (n=1) and were treated with 5 mg of an aminoglycoside administered daily through an Ommaya or Rickhan reservoir. The CSF aminoglycoside concentrations ranged from 12.8–40 μg/mL within the first six hours after administration. Concentrations remained between 4–6 μg/mL for most of the following 18 hours. No toxicities were reported in any episode.

Wald and McLaurin described eight patients (ages 1 month to 19 years) with a shunt infection or ventriculitis who were successfully treated with systemic and IVT administration of gentamicin.[14] IVT gentamicin was dosed at 1–6 mg daily (six patients) or every other day (two patients) for 4-16 days. Gentamicin CSF concentrations ranged from 5.3–12.6 μg/mL at 24 hours post-dose. These concentrations were 1.6–42 times above the MIC of the causative organisms. No seizures, neurological deficits, or other toxicities were seen with the administration of intraventricular gentamicin.

Controlled studies of the use of IT and IVT antibiotics in neonates have been performed. The Neonatal Meningitis Cooperative Study Group was formed to evaluate the role of IT- administered antimicrobials in the treatment of gram-negative meningitis.[13] This multicenter, prospective, randomized controlled trial evaluated 117 infants with gram-negative meningitis. Causative organisms included *E coli* (n=82), *Salmonella* sp. (n=7), *Citrobacter diversus* (n=5), *Proteus mirabilis* (n=5), *Serratia* sp. (n=5), *Klebsiella* sp. (n=4), *Enterobacter* sp. (n=4), and *P aeruginosa* (n=1). [note: total = 113] All patients received systemic antibiotics, and 52 patients received concomitant IT gentamicin. IT therapy (1 mg daily) was administered for a minimum of three days or until CSF cultures became sterile. CSF gentamicin concentrations were measured at two to four hours after a 1-mg ITdose in four infants. The authors did not specify concentration goals,

but did report that CSF concentrations were 18.4, 25, 36.8, and >40 μg/mL. CSF samples from 43 infants showed gentamicin concentrations that ranged from 0.5–3.4 μg/mL at 18-24 hours after a 1-mg IT dose. The authors did not report an infection eradication rate but stated 80 (68.4%) of the 115 infants survived. The addition of IT antibiotics to systemic therapy for meningitis did not improve patient outcomes in this study. Twenty-one (32%) infants on systemic antibiotics alone and 14 (28%) infants receiving IT plus systemic antibiotics died secondary to meningitis. Mortality rates did not differ significantly between the two groups (P=0.769). Additionally, there was no correlation between causative organisms and mortality rate in either group. No acute adverse effects were seen with IT gentamicin, but one infant who received three days of this therapy developed hyperreflexia and left lower extremity weakness 12 months after therapy. The child showed some neurologic improvement but was still impaired at three and one half years of age.

Subsequently, the Second Neonatal Meningitis Cooperative Study Group examined the role of IVT administration of gentamicin.[15] They hypothesized that the IVT route would sterilize the CSF quickly and decrease meningitis case-mortality rates. This multicenter, prospective, randomized controlled trial included 71 infants diagnosed with gram-negative meningitis with or without ventriculitis (n=52 and n=19, respectively). Twenty-eight of the 52 infants with ventriculitis were randomized to receive 2.5 mg/day of gentamicin IVT for a minimum of three days in conjunction with systemic antibiotics. In addition to systemic antibiotics, 10 of 19 infants without ventriculitis were randomized to receive IT gentamicin 2.5 mg daily for a minimum of three days. Infants who received IVT therapy had gentamicin CSF concentrations ranging from 10–130 μg/mL and 1–24 μg/mL, 1-6 hours and 16-24 hours post-dose, respectively. This study was discontinued because of increased mortality in patients who received IVT antibiotics when compared to systemic antibiotics alone. In the patients with ventriculitis, 12 (42.9%) infants who received IVT died versus three (12.5%) infants receiving systemic therapy alone (P=0.016). In the subset of patients without ventriculitis, no deaths were seen in the nine patients who received IT antibiotics, but two patients who only received systemic therapy died. Overall mortality was higher in the patients with meningitis and ventriculitis (29%) versus patients with meningitis alone (10.5%). The authors' explanations for this high mortality rate with IVT therapy included the presence of resistant organisms, cyst formation from repeated ventricular taps, or gentamicin toxicities. The outcome of this study provides the greatest concerns regarding the administration of IVT antibiotics and warrants their cautious use.

Individualized therapy is necessary for all patients being administered intraventricular antibiotics. The presence of hydrocephaly, an Ommaya reservoir, or a VP shunt complicates dosing regimens. Patients with a lower degree of hydrocephalus than our patient may require lower doses of IVT antimicrobials due to a decreased volume of distribution. Also, removal of CSF through repeated intermittent sampling or continuous drainage may alter drug clearance and distribution. Administration technique may also impact drug distribution in patients with shunts. A rapid, forceful injection may open the valve and deliver the drug into the distal shunt or peritoneal cavity.[8] However, a slow, gentle injection will ensure that the drug enters the ventricles.[8] Wright and colleagues evaluated the pharmacokinetics of amikacin and found a large variation in the volume of distribution and clearance.[16] They correlated large CSF volumes with hydrocephalus, meningomyelocele, and occipital abscess and recommend individualizing patient dose and regimen.

The use of IT and IVT antibiotics does not go without reservation – particularly in children with developing nervous systems. Nephrotoxicity and ototoxicity are well-documented adverse effects that are associated with systemic use of all aminoglycosides. Previous experience indicates potential risks of administering IVT aminoglycosides.[1,8,12,13,15-18] Yeung reported an infant who exhibited signs of deafness during the fifth week of therapy for *E coli* meningitis.[12] The infant was only receiving systemic gentamicin and ampicillin, but had previously received 20 days of IVT and 16 days of IT gentamicin therapy. The systemic gentamicin was discontinued when the infant failed to respond to rattles and a music box as he had earlier during therapy. No objective hearing tests were performed at the time, but follow-up with audiometry testing at 2.5

years of age was normal.

Neurologic and morphologic changes have also been reported in adult patients and animals.[17-19] Incidental findings in an adult at autopsy revealed multiple brainstem lesions. This patient was previously treated with IV and IT gentamicin for *P aeruginosa* meningitis.[17] Neuropathological changes have also been seen in rabbits after intracisternal and IVT administration of gentamicin.[17,18] It is unclear how toxicities from IVT or IT aminoglycoside administration may affect the growth and development of the premature infant brain.

Target serum tobramycin peak and trough concentrations in our patient were 6–8 μg/mL and <2 μg/mL, respectively. Due to a lack of standard dosing, the degree of hydrocephalus, and risk of adverse effects, we initiated IVT therapy with 2 mg of tobramycin. Our target CSF trough tobramycin concentration was 20–30 μg/mL. After 4 days of IVT therapy, the CSF tobramycin concentration rose to 32.4 μg/mL, and the dose was reduced to 1.5 mg. At this time, the patient was clinically improving and the CSF was sterilized. (CSF cultures showed no growth.) When three successive CSF cultures were reported as no growth, the IVT tobramycin was discontinued. No evidence of acute adverse effects (e.g., nephrotoxicity, seizures) or secondary infections were noted following IVT or IV tobramycin. Testing for ototoxicity was not performed due to eventual death of the infant.

CONCLUSION

The lack of medically based evidence to support the use of IVT antibiotic mandates that caution be exercised any time this route of administration is employed. Intraventricular therapy may be used as a treatment of "last resort" for patients in whom aggressive conventional therapy fails to eradicate gram-negative meningitis or in those whose infecting organism is only susceptible to antimicrobials that have poor CNS penetration.[1] Potential neurological complications in the premature infant warrant a careful assessment of the risks and benefits of IVT antibiotic therapy before this therapeutic modality is used.

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