ABSTRACTS FROM THE LITERATURE

ANTIPYRETIC EFFICACY AND SAFETY OF IBUPROFEN AND ACETAMINOPHEN IN CHILDREN. Goldman R, Ko K, Linett L, et al. Ann Pharmacother 2004;38:146-50.

Background: Efficacy and safety questions surrounding IBU (ibuprofen) and APAP (acetaminophen) are not new, but a recent FDA campaign has again brought this topic to the forefront in pediatric clinicians' minds. Initiated January 22, 2004, the FDA's goal of this educational launch was to focus on the safe use of OTC pain and fever reducers. Thus, pharmacists and doctors are frequently asked questions about which agent, IBU or APAP, is best to treat fever. The answer to this question is not clear-cut and the evidence-based medicine must be examined to gather both safety and efficacy data that are necessary to make an appropriate decision. Goldman and colleagues set out to accomplish the aforementioned task by publishing a review article in the January 2004 edition of The Annals of Pharmacotherapy.

Objectives: The goal of this article was to evaluate the current data concerning the antipyretic effects of IBU and APAP. Secondly, this paper set out to address and assess the adverse effects associated with the use of these agents in children.

Methods: An extensive literature search utilizing the terms IBU and APAP were completed using the MEDLINE and EMBASE databases. Only comparative studies written in English that contained subjects ages birth to 18 years old were examined. Bibliographies of selected articles were also examined in order to ensure a comprehensive collection of the literature had been obtained.

Results: Fourteen studies were found via the above search methodology. Eleven of these studies were randomized control trials. The trials evaluated a variety of outcome measures to compare the antipyretic effects of ibuprofen and acetaminophen. Studies included investigations of single and/or multiple dose therapies. Adverse effects were also noted.

IBU exhibited greater antipyresis and longer duration of effect when compared to APAP in four studies. Several other studies found no significant difference in the single-dose antipyretic effect of ibuprofen and acetaminophen when measuring change in temperature over time, duration of temperature reduction, and extent of temperature reduction. A multiple dose study using recommended dosages of both drugs (ibuprofen 10 mg/kg, acetaminophen 15 mg/kg) found ibuprofen to produce a larger reduction in temperature up to 6 hours after administration. The area under the curve (AUC) of percent temperature reduction over time was significant ($P = 0.03$), but the difference appeared to disappear when measured at 0–12 hours ($P = 0.06$), 0–24 hours ($P = 0.07$), or 0–48 hours ($P = 0.13$).

Contradicting information exists when examining the evidence about adverse effects of these two agents. Even though there is ample information about each of these medications separately, comparison information is limited. From the available literature the review article states that the risk for hospitalization due to gastrointestinal bleeding, renal failure, or anaphylaxis was not increased following short-term use of ibuprofen. Other studies have reported adverse effects in 0–26.6% of febrile children treated with ibuprofen compared with 0.9–19% treated with acetaminophen. Goldman and colleagues highlighted one study that stated subjects receiving IBU had at least one adverse event more than those receiving APAP.

Important to note is the varied dosages of the antipyretics across studies, ranging from 0.5 to 10 mg/kg with ibuprofen and 8 to 15 mg/kg with acetaminophen. Results of studies that used doses lower than those recommended therapeutically should not be extrapolated to clinical practice. Other limitations noted by the authors included the small sample size in the majority of the comparison studies. Also, differing population characteristics including treatment setting, severity, course and management make it difficult to draw any strong conclusions about IBU and APAP.

Conclusions: Goldman and colleges summarized that the antipyretic effectiveness of IBU compared to APAP remains disputable. They state that more trials are needed to examine this topic. From an efficacy standpoint IBU could be superior, but there are numerous limitations in the literature that the authors reviewed. Furthermore, the paper concludes that safety concerns surrounding these agents do exist, and can be considered modest with short term use. Adverse events looking at aspects including concomitant or prolonged use

with IBU and APAP were not discussed.

Discussion/Comments: This article poses the question of how acetaminophen and ibuprofen compare in terms of antipyretic efficacy in children. The review highlights the evidence based medicine that attempts to find a definite answer to this inquiry. Each clinician must weigh the benefits and risks of using antipyretic medications. Not only is there debate about which agent to use and which dosing regimen to prescribe, there are definite concerns regarding adverse events due to use of these agents. Currently, our institution recommends use of either agent exclusively with appropriate monitoring. Children that are dehydrated, with renal dysfunction, or at risk for gastrointestinal bleeding should not receive IBU. Education is key in proper utilization of these agents.

REFERENCES

1. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA 1995; 273:929-33.
2. American Academy of Pediatrics. Acetaminophen toxicity in children. Pediatrics 2001;108:1020-4.
3. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. Pediatrics 1999;104:e39.
4. http://www.fda.gov/cder/drug/analgesics/letter.htm (FDA website) accessed Jan 2004.
5. Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. Am J Dis Child 1992;146:626-32.

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TREATMENT OF OTITIS MEDIA WITH OBSERVATION AND A SAFETY-NET ANTIBIOTIC PRESCRIPTION. Siegel RM, Keily M, Bien JP, et al. Pediatrics 2003;112:527-31.

Background: Between 1980 and 1992, prescriptions for acute otitis media (AOM) doubled from 12 million to 24 million, and AOM is one of the most common diagnoses in children.[1] Recent studies have shown that 78% of untreated children with uncomplicated AOM had resolution of symptoms within 4 to 7 days.[2]

Objective: To determine if: 1) parents and physicians in the US would be comfortable with safety-net antibiotic prescriptions (SNAP) for AOM and 2) if SNAP could decrease antibiotic usage.

Methods: Children ages 1-12 with AOM were eligible for inclusion. Offices of the Cincinnatti Pediatric Research Group (11/25) participated in the study. Once enrolled, parents received a form that included demographic data, physical exam findings, treatment regimen, and an appropriate SNAP, which was only to be filled within 5 days. Parents were to fill the SNAP if the child's symptoms did not improve in 48 hours. At enrollment, samples of ibuprofen, acetaminophen, and antipyrene/benzocaine otic drops were provided in the physician's office. Five to 10 days after enrollment, a nurse conducted a structured telephone interview to determine if the SNAP had been filled, if the child was progressing, and the parents' perception of SNAP.

Results: A total of 194 patients were enrolled, and 90% completed the follow-up interview. Of the 175 enrollees, the average age of the child was 5 years (44% were female). Sixty-nine percent of the parents did not fill the SNAP (n = 120), and most said that they would be willing to treat with analgesics and antipyretics in the future. The 55 enrollees who filled the SNAP (33 within 48 hours) did so because of continued pain or fever, sleep disruption, no reason, and missed days of work or child care. The only variable which explained parents' decision to fill SNAP was > episodes of AOM previously.

Adverse Events: Although no complications were reported as a result of this study, the case of one patient is notable. A 16-month-old who was diagnosed with AOM and given a SNAP (filled after 48 hours) went on to develop AOM in the opposite ear 6 weeks later, followed by postauricular cellulites. He responded to intravenous antibiotics and did not develop any further complications.

Conclusions: The results of this study seem to support the conclusion that for uncomplicated AOM, treatment with pain and antipyretic medications alone with a SNAP is appropriate, and that a certain population of parents find this to be acceptable.

Comments: Bacterial resistance is an ever growing problem in the US. Duchin and colleagues

found that more than half of *Stretococcus pneumoniae* from nasopharyngeal swabs of children who attended daycare in 1 community were penicillin-resistant.[3] A survey by Watson and colleagues showed that although 97% of physicians recognize that overuse of antibiotics contributes to resistance, 46% will still prescribe an antibiotic for the common cold.[4] Additionally, Palmer and Bauchner surveyed a group of parents and found that 85% of them realized that antibiotics were overused, but 93% of them still felt that an antibiotic was necessary for the treatment of AOM.[5]

These studies highlight the importance of changing practices when appropriate in order to prevent further antibiotic resistance. Future studies regarding this issue need to be conducted over longer periods of time with larger and more diverse groups of patients. Weaknesses in this study include a small population, lack of diversity, a brief follow-up period, and heavy reliance on subjective criteria. Additionally, a clear definition of AOM should be determined across the board for all practitioners, as each of the studies evaluating AOM have had somewhat different criteria. Longer term studies are needed to evaluate the rate of recurrence or complications in patients who are and are not treated immediately with antibiotics.

REFERENCES

1. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995;273:214-9.
2. Takata GS, Chan LS, Shekelle P, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media: I. The role of antibiotics in treatment of uncomplicated acute otitis media. Pediatrics 2001;108:239-47.
3. Duchin JS, Breiman RF, Diamond A, Lipman HB, Block SL, Hedrick JA, et al. High prevalence of multi-drug-resistant streptococcus pneumoniae among children in a rural Kentucky community. Pediatr Infec Dis J 1995;14:745-50.
4. Watson RL, Scott SF, Jayaraman M, Keyserling H, Koczak, Schwartz B. Antimicrobial use for pediatric upper respiratory infections: reported practice, actual practice, and parent beliefs. Pediatrics 1999;104:1251-7.
5. Palmer DA, Bauchner H. Parents' and physicians' views on antibiotics. Pediatrics 1997; 99e6. Available at: http://www.pediatrics.org/cgi/content/full/99/6/e6. Accessed on August 29, 2004.

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BACTERIOLOGIC AND CLINICAL EFFICACY OF ORAL GATIFLOXACIN FOR THE TREATMENT OF RECURRENT/NONRESPONSIVE ACUTE OTITIS MEDIA: AN OPEN LABEL, NONCOMPARATIVE, DOUBLE TYMPANOCENTESIS STUDY.

Leibovitz E, Piglansky L, Raiz S, Greenberg D, Hamed K, Ledeine J, Press J, Leiberman A, Echols R, Pierce P, Jacobs M, Dagan R. Pediatr Infect Dis J, 2003;22:943-9.

Background: Acute otitis media (AOM) is the most common disease of childhood with eighty percent of children experiencing at least one episode in the first year of life.[1] The number of office visits for otitis media increased from 9.9 million visits in 1975 to 24.5 million in 1990 corresponding to more than 20 million prescriptions written for otitis media-related antimicrobials.[2] Recurrent AOM is characterized by at least 3 episodes in 6 months or 4 episodes in 12 months and occurs in approximately 20 to 30 percent of the pediatric population.[1] It should be distinguished from persistent or nonresponsive AOM, which is characterized by persistence of signs and symptoms of middle ear infection after 48 to 72 hours of antibiotic therapy and/or relapse of the current episode of AOM within one month of completion of antibiotic therapy. The pathogen responsible for causing a recurrent episode of AOM may be different than the original pathogen, whereas nonresponsive AOM is simply treatment failure. The most common pathogens associated with recurrent and persistent AOM are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* with *Staphylococcus aureus* and *pyogenes* infections occurring less commonly. The proportion of β-lactamase-producing *Haemophilus influenzae* and multi-drug resistant *Streptococcus pneumoniae* is growing, therefore making judicious use of antimicrobial agents essential. Currently three antibiotics are recommended for the treatment of recurrent and persistent AOM

by the Centers for Disease Control Drug Resistant *Streptococcus pneumoniae* Working Group: (1) amoxicillin/clavulanate (80-90 mg/kg/day); (2) cefuroxime axetil (30 mg/kg/day); and (3) ceftriaxone IM (50 mg/kg × 3 days).[3] Recently, the fluoroquinolones have been evaluated as potential alternatives for treating recurrent AOM due to their activity against the main pathogens involved, but the arthrotoxicities seen in juvenile animal models are a major concern with their use in children.

Objective: To determine the bacteriologic and clinical efficacy of gatifloxacin in recurrent/nonresponsive AOM and to document the nature of adverse events in children.

Methods: 160 patients were enrolled in this open label, noncomparative, double typanocentesis study performed at Soroka University Medical Center in Beer-Sheva, Israel. The patients ranged in age from 6 months to 4 years old with the majority of patients being less than one year of age. Patients were included if inclusion criteria for recurrent and/or nonresponsive AOM were met. The authors defined recurrent AOM as 3 episodes in 6 months or 4 episodes in 12 months. Nonresponsive or persistent AOM was defined as AOM occurring 14 days after completing antibiotic treatment or symptoms not improving after 48 hours of antibiotic therapy. Exclusion criteria included: body wt > 40 kg, spontaneous perforation of the tympanic membrane and drainage for > 24 hrs, presence of tympanostomy tubes, anatomic abnormalities, serious underlying disease (neoplasm, cystic fibrosis, juvenile diabetes mellitus, cardiac dysrhythmia), concomitant infection, renal or hepatic insufficiency, hypersensitivity to fluoroquinolones, present or previous joint abnormalities, or the use of any investigational drug, vaccine, or device within 30 days. Gatifloxacin suspension (10 mg/kg once daily) was prescribed for 10 days. An otolaryngologist performed tympanocentesis and middle ear fluid cultures before the first dose of study medication was given. If a pathogen was identified, tympanocentesis was repeated on Day 4, 5 or 6 of treatment. Additional tympanocentesis was performed in cases of recurrent AOM during the follow-up period. Clinical and otologic assessments were also performed on Day 4, 5 or 6, at the end of therapy (Day 12, 13 or 14) and at the follow-up visit (between Days 22 and 28). Rheumatologic histories were taken and joint examinations were conducted at each visit.

Results: 98% of patients received at least 1 antibiotic course before starting the study, 24% received > 1 antibiotic course, and 50% received antibiotics in previous 24 hours. Amoxicillin was administered in 53% of patients in the prior month, amoxicillin/clavulanate in 33%, cefuroxime axetil in 21%, ceftriaxone in 16%, and azithromycin in 8% of patients. 128/160 patients completed the study. Of the 32 patients that discontinued treatment early, 17 patients experienced an adverse event, 10 patients were lost to follow-up, 3 patients withdrew their consent, and 2 patients discontinued treatment due to laboratory abnormalities. Discontinuation of therapy due to adverse events was required because of vomiting (n = 15), diarrhea (n = 3), dehydration (n = 2), and maculopapular rash (n = 2). No articular toxicity was observed during therapy or during the follow-up period. There were 89 microbiologically evaluable patients and 121 isolates recovered: 74 *H. influenzae*, 36 *S. pneumoniae*, 9 *M. catarrhalis*, and 2 *S. pyogenes*. 26 of 36 (72%) of the *S. pneumoniae* isolates were nonsusceptible to penicillin with 15 being fully resistant. 19% of *H. influenzae* produced b-lactamase. Gatifloxacin demonstrated 100% eradication of *H. influenzae*, 94% *S. pneumoniae*, 100% *M. catarrhalis*, 50% *S. pyogenes* (2 patients) corresponding to 98% overall eradication (118/121). For patients with recurrent AOM only and nonresponsive AOM only, the cure rates were 86% and 91% respectively. The cure rate was 91% for patients with both recurrent and nonresponsive AOM. There were 3 bacteriologic persistences: 2 with *S. pneumoniae* and 1 with *S. pyogenes*. 114/160 patients were considered clinically evaluable at end of therapy (Day 12 to 14). Of these 114 patients, 103 were considered to have achieved clinical success. For the remaining 11 patients classified as clinical failures on Day 12 to 14, one patient had an associated bacteriologic failure on Day 4 to 6. In the remaining 10 patients, the episode of AOM diagnosed on Day 12 to 14 occurred after bacteriologic eradication on Day 4 to 6. Overall, there were 31 episodes of recurrent AOM occurring after completion of therapy.

Conclusions: The authors concluded that gatifloxacin is efficacious and safe for the treatment of recurrent/nonresponsive AOM.

Comments: The authors clearly state that gatifloxacin has no place for simple acute otitis

media or even as a routine second-line agent. High-dose amoxicillin still remains the first-line treatment of choice for uncomplicated AOM according to the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group.[3] For patients with clinically defined treatment failure after 3 days of therapy, amoxicillin/clavulanate, cefprozil, or ceftriaxone should be used before considering gatifloxacin. Gatifloxacin is an attractive alternative for recurrent AOM due to its activity against many pathogens including *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae,* and *Moraxella catarrhalis.* It is estimated that 1.5% of outpatient quinolone usage and 136,000 prescriptions annually are prescribed for children and adolescents (0 to 18 years of age). Based on drug-associated arthralgia reporting to the FDA, quinolone-treated children would represent 2 cases per 100,000 filled prescriptions. A similar trial was published in the same issue of the *Pediatrics Infectious Disease Journal* performed by Arguedas and colleagues which evaluated 254 patients, ages 6 months to 7 years of age.[4] The patients received gatifloxacin suspension (10 mg/kg once daily for 10 days) for recurrent/nonresponsive AOM. Similar results were seen in both trials, but missing from the Leibovitz trial that was present in the Arguedas trial were short and long-term safety arms. Patients were followed up 4 weeks after treatment and also 2, 4, 6, and 12 months after treatment with gatifloxacin. After 4 weeks of treatment, only 2 patients experienced arthrotoxicity and both episodes were considered transient. One patient was a 3 year-old with knee pain and abnormal gait, which resolved in 13 days. The other patient was a 5 year-old with mild bilateral hand and foot pain that occurred after one dose of study medication and considered unlikely related to the drug. The results of the long-term safety arm will be published separately. Concerns of resistance may be of more importance than the arthrotoxicity potential associated with fluoroquinolones in children. On May 10, 2004, the FDA's Anti-infective Drugs Advisory Committee was scheduled to review the use of gatifloxacin for recurrent otitis media, however that meeting was cancelled. If approved by the FDA for use in recurrent/nonresponsive AOM, gatifloxacin may be another alternative agent for children who have received multiple courses of antibiotics without resolution.

REFERENCES

1. Pichichero ME. Recurrent and persistent otitis media. Pediatr Infect Dis J 2000;19:911-16.
2. Schappert SM. Office visits for otitis media: United States, 1975-90. Adv Data 2002;328:1-32.
3. Dowell SF, Butler JC, Giebink GS, Jacobs MR, Jernigan D, Musher DM, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance-a report from the Drug-resistant Streptococcus pneumoniae Therapeutic Working Group. Pediatr Infect Dis J 1999;18:1-9.
4. Arguedas A, Sher L, Lopez E, Saez-Llorens X, Hamed K, Skuba K, Pierce PF. Open label, multicenter study of gatifloxacin treatment of recurrent otitis media and acute otitis media treatment failure. Pediatr Infect Dis J 2003;22:949-55.

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REASSESSMENT OF THEOPHYLLINE USE FOR SEVERE ASTHMA EXACERBATION: IS IT JUSTIFIED IN CRITICALLY ILL HOSPITALIZED PATIENTS? Self TH, Redmond AM, Nguyen WT. J Asthma 2002;39:677-86

The use of theophylline and related medications in the treatment of asthma has been in question since the introduction of β2-adrenergic receptor (β2AR) agonists. Self et al. recently reviewed the contemporary literature assessing the role of theophylline in severe asthma exacerbations.1 The authors discuss studies using theophylline with and without benefit and note a trend that does not favor theophylline. Most importantly, these reports usually do not study the drug in the severely ill asthmatic, an extremely difficult population. From these data, Self, et al. conclude that theophylline does have a role in treating severe asthma exacerbations in patients who do not respond to maximal therapy with β2AR agonists and systemic corticosteroids.[1]

Based on data presented in this review and other investigations of theophylline and related drugs, using these medications for treatment-refractory

asthma is logical from both a clinical standpoint and from a pharmacologic view. Focusing on asthma, β2-receptor agonists exert their action by stimulating the membrane-bound β2-receptor in the smooth muscle of the respiratory tract.[1,2,4] The family of β-adrenergic receptors are linked to intracellular G proteins that activate adenylyl cyclase. Adenylyl cyclase converts ATP (adenosine triphosphate) to cAMP (cyclic adenosine monophosphate), a second messenger that activates protein kinase A. Protein kinase A activates or inactivates enzymes, receptors, and other proteins via phosphorylation, resulting in smooth muscle relaxation and bronchodilation.

However, when a patient does not respond to β2AR-agonists during an acute asthma attack, there is a need to augment the activity of these drugs. Methylxanthines such as theophylline and caffeine were once the favored treatment for asthma until the advent of β2-receptor specific antagonists. Methylxanthines were long thought to exert their action by inhibiting cyclic nucleotide phosphodiesterase enzymes, which catalyze the breakdown of cAMP. However, phosphodiesterase inhibition does not occur at clinically relevant concentrations, and researchers have proposed several clinically relevant mechanisms of these drugs, including adenosine receptor inhibition, increased secretion of epinephrine, and increased secretion of IL-10 (an anti-inflammatory mediator) among others.[5]

The most prominent mechanism of theophylline is its competitive antagonism of a specific adenosine receptor subtype.[6] Studies with theophylline demonstrate that this drug binds to adenosine receptors with a range of affinities, based on receptor subtype (discussed later).[5] Adenosine is a purine transmitter with a myriad of effects throughout the body both peripherally and in the central nervous system. In an acute asthma exacerbation, adenosine likely does not exert significant direct action on bronchial smooth muscles, but it may cause bronchoconstriction via increasing release of inflammatory mediators from lung mast cells.

Four subtypes (A1, A2A, A2B, and A3) of adenosine receptor have been identified.[5] Agonism of the adenosine A1 receptor leads to bronchoconstriction in animal models, but the role of adenosine A1 receptors and their antagonists is unclear in the pathophysiology of human asthma.[5] Activation of adenosine A2A receptors seems to suppress neutrophil activation and may promote an endogenous anti-inflammatory mechanism.[5] Animal adenosine A3 receptors do not share a large degree of genetic similarity with human adenosine A3 receptors, and the role of this subtype of adenosine receptors in humans has not been completely described.[5]

The adenosine A2B receptor subtype is the focus of much attention in the treatment of asthma. Adenosine A2B receptors have been noted to be present on respiratory smooth muscle cells and mast cells, in addition to other cells throughout the body. It is believed that agonism of bronchial muscle and mast cell adenosine A2B receptors is prominent in the pathophysiology of asthma.[5] Thus, highly specific antagonists of adenosine A2B receptors may soon be fundamental to the prevention and/or treatment of asthma.[5]

Based on the data presented by Self et al. and other authors, theophylline seems to provide clinical benefit in asthma patients who are severely ill and who are not responding to aggressive doses of traditional asthma therapies (i.e., inhaled β2AR agonists and systemic corticosteroids).[1] In order to determine why some patients do not respond to β2-agonists and corticosteroids, more research is needed. Several theories explain the lack of response to conventional asthma treatment.

One of the causes of poor response to β-agonists may be desensitization or down-regulation of β-receptors after regular, prolonged use of β-agonists. There are multiple mechanisms believed to contribute to decreased response to β-adrenergic receptor agonists.[7] In the short term, phosphorylation of the transmembrane subunits of the receptor leads to uncoupling from the Gs protein, resulting in lack of responsiveness.[7] This phosphorylation is accomplished by β-adrenergic receptor kinase (bARK) and protein kinase A. bARK identifies β-agonist receptors that are occupied; thus, the frequent, regular use of β-receptor agonists contributes to the activity of this enzyme, resulting in uncoupling of the receptor from the G-protein subunit. Another process in down regulation of β2AR is related to the mechanism of the receptor itself. β2AR is internalized after binding a β-receptor agonist and is either metabolized or returned to the cell surface only after the agonist has left the binding site. Thus, receptor turnover rate dictates the availability of receptors on the cell surface. It is possible that long-term use of β2AR agonists decreases b-adr-

energic receptor turnover via inhibition of gene transcription.[7]

Another consideration in the discussion of treatment-resistant asthma that has been receiving much attention recently is the occurrence of genetic polymorphisms of the β2AR. A recent review of β2AR polymorphisms in this journal provides an excellent background for understanding why some patients do not respond to standard asthma therapies as well as others.[8] The most commonly noted polymorphisms affect the influence of catecholamines and β2-agonists on down-regulation in some places, it is hyphenated and others not. I think we hyphenated it in past issues. I am not on the computer I usually work from, so I can't check past issues at the moment of β-receptors. Interestingly, a combination of certain genetic codes confers absolute resistance to down-regulation of β-receptors. The ramifications of genetic polymorphisms on response to drug therapy in asthma or any disease state will clearly shape the future of therapeutics.

In conclusion, the addition of theophylline to the standard therapeutic regimen for acute, severe, refractory asthma is a proper approach. Based on the pharmacologic mechanisms of β2AR agonists and methylxanthines, the addition of theophylline is expected to provide significant benefit in patients with acute asthma not relieved by β2AR agonists and corticosteroids. Genetic differences among patients may dictate response to drug therapy, and this area of specialty deserves much attention.

REFERENCES

1. Self TH, Redmond AM, Nguyen WT. Reassessment of theophylline use for severe asthma exacerbation: is it justified in critically ill hospitalized patients? J Asthma 2002;39:677-86.
2. Young M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child 1998;79:405-10.
3. Ream RS, Loftis LL, Albers FM, Becker BA, Lynch RE, Mink RB. Efficacy of IV theophylline in children with severe status asthmaticus. Chest 2001;119:1480-8.
4. Roberts G, Newsom D, Gomez K, Raffles A, Saglani S, Begent J, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomized controlled trial. Thorax 2003;58:306-10.
5. Fozard JR, Hannon JP. Adenosine receptor ligands: potantial as therapeutic agents in asthma and COPD. Pulm Pharmacol Ther 1999;12:111-4.
6. Undem BJ, Lichtenstein LM. Drugs used in the treatment of asthma. In: Hardman JG, Limbird LE, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York, NY: McGraw-Hill, 2001.
7. Barnes PJ. Beta-adrenergic receptors and their regulation. Am J Respir Crit Care Med 1995;152:838-60.
8. Binaei S, Rashed SM, Christensen ML. β2-Adrenoreceptor polymorphisms in asthmatic patients. J Pediatr Pharmacol Ther 2003;8:22-8.

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