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YAFFE AWARD LECTURE

Advocating for Patients Through Clinical Research

Leslie Hendeles, PharmD

Departments of Pharmacy Practice and Pediatrics, The University of Florida, Gainesville, Florida

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INTRODUCTION

Dr. Sumner Yaffe is the father of pediatric pharmacology. In the 1970s he led a clinical pharmacology consultation service at Buffalo's Children's Hospital that incorporated a clinical pharmacist, Greg Chudzig, on his team. He was among the first physician Clinical Pharmacologists to recognize the potential contributions of a clinical pharmacist to optimizing drug therapy in patients and teaching clinical pharmacology to pediatric interns and residents. He subsequently edited the first text on pediatric clinical pharmacology and I had the honor of collaborating with Dr. Miles Weinberger, a Pediatric Allergist/ Pulmonologist at the University of Iowa, on a chapter on theophylline for that book. Later as Director of the NIH Institute of Maternal and Child Health, he was instrumental in securing funding for a network of pediatric clinical research units in the United States, among other notable accomplishments. Even now in his retirement, Dr. Yaffe continues to educate pediatricians in training on clinical pharmacology as a Visiting Professor at the University of California, Los Angeles.

It is an outstanding honor to be the 2007 recipient of this esteemed award. I consider this the most important recognition of my contribution to improving the use of drugs in children and serving as a patient advocate. The Award Committee asked me to present at the Pediatric Pharmacy Advocacy Group meeting what I thought were my most important contributions. A summary of that presentation follows.

Address correspondence to: Leslie Hendeles, PharmD, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0486, email: hendeles@cop.ufl.edu

THEOPHYLLINE

In 1973, Mitenko and Ogilvie published a report in *The New England Journal of Medicine* on a pharmacokinetic basis of dosing intravenous aminophylline in hospitalized patients with acute asthma.[1] They concluded from a study of nine patients that a 5.6 mg/kg loading dose followed by a constant IV infusion of 0.9 mg/kg/hr would result in plasma theophylline concentrations of approximately 10 □g/mL for 95% of patients. This dosing recommendation was then adopted by physicians across the country.

ABBREVIATIONS CF, cystic fibrosis; CFC, chlorofluorocarbons; FDA, Food and Drug Administration; MDI, metered-dose inhaler; VHC, valved holding chamber

Before the publication of this report, I had set up a theophylline blood concentration monitoring service in the University of Iowa, College of Pharmacy with the help of Drs. Lyle Bighley and John Locke, Pharmaceutics Professors. In collaboration with Robert Richardson, MD, then Director of the Medical Intensive Care Unit, I was monitoring theophylline concentrations and recommending dosage adjustments when the Mitenko and Ogilvie recommendation was adapted. Much to our surprise, this dosing regimen resulted in excessive theophylline concentrations and frequent toxicity (Figure 1).[2] In calculating theophylline clearance for these patients, we found that toxic concentrations in 17 of the 49 patients were a result of reduced clearance. The apparent reason for the discrepancy between our findings

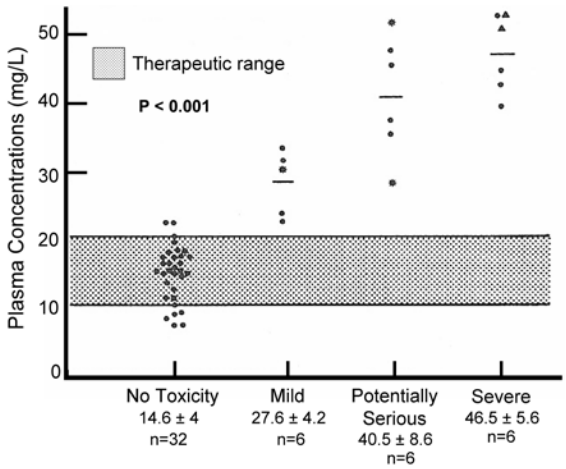

Figure 1. Theophylline plasma concentrations measured in 49 critically ill adults after an IV aminophylline loading dose of 5.6 mg/kg followed by a constant infusion of 0.9 mg/kg/hr. Concentrations were significantly higher in the three groups with toxicity. Reproduced with permission from the *Annals of Pharmacotherapy.* [2]

and the Mitenko and Ogilvie report was that patients in their study were relatively young cigarette smokers with higher and less variable clearances than the seriously ill medical intensive care unit patients that we monitored. We suspected numerous factors that reduced theophylline clearance including heart failure and liver dysfunction, and subsequently others confirmed these findings.[3-8] Clearly, the most important lesson of this experience was the need to individualize dosage to compensate for variation in clearance and the danger in calculating dosing regimens in one population and extrapolating them to other populations.

We presented the results of our study to a Food and Drug Administration (FDA) Pulmonary Allergy Drugs Advisory Committee, and subsequently the Agency issued guidelines on dosing IV aminophylline. Since theophylline was available in various formulations by different manufacturers, the Agency developed a standardized labeling that all manufacturers were subsequently required to include in their package inserts.

In the late 1970s and early 1980s, slow-release theophylline was the first line maintenance medication for reducing the frequency and severity of symptoms in patients with persistent asthma. This was before the recognition of the inflammatory component of asthma and the subsequent shift to the use of inhaled corticosteroids as first-line therapy.

At that time, there were a large number of theophylline products available, and Dr. Weinberger and I had previously demonstrated wide variation in the rate and extent of theophylline absorption from these products.[9-11] Bioavailability studies indicated that the ability to maintain a theophylline concentration within the 10-20 μg/mL therapeutic range was dependent upon the rate of metabolism in the patient (clearance), the rate and extent of absorption of the product, and the dosing interval selected by the prescriber.[11] TheoDur (Key Pharmaceutical, Kenilworth, NJ) became the most frequently prescribed slow-release product in the United States and required an every-12-hours dosing interval in most adults and every-8-hours in children who, on average, had higher clearance rates than adults.

Subsequently, FDA approved Theo-24 (UCB Pharma, Inc, Smyrna, GA) based upon company claimes that the product could be given once a day due to bioavailability studies in non-smoking adults (who on average slowly metabolize theophylline).[12] At that time, FDA required bioavailability studies to be conducted in the fasting state. However, Dr. Weinberger and I were incredulous that any slow-release product could maintain therapeutic concentrations for a 24-hour period, especially in patients who were more rapid metabolizers. We noted that the dose employed in one Searle bioavailability study was 1500 mg, which suggested to us that Theo-24 had incomplete absorption since previous data indicated that the median dose required to produce a therapeutic concentration in non-smoking adults was 900 mg/day.[13] We hypothesized that food would further reduce the extent of absorption and conducted a crossover study in 8 healthy non-smoking volunteers. Much to our surprise, we discovered that food induced dose-dumping of this product—that is, 48% of the dose was released in a 4-hour period when taken with food compared to 18.5% when taken fasting (Figure 2).[14] The most likely explanation for this finding was the pH sensitive dissolution of the coating on the Theo-24 beads. In the postprandial alkaline pH of the small intestine, the coating dissolves faster than when taken fasting when the pH is lower.

Subsequently, in a study on the circadian

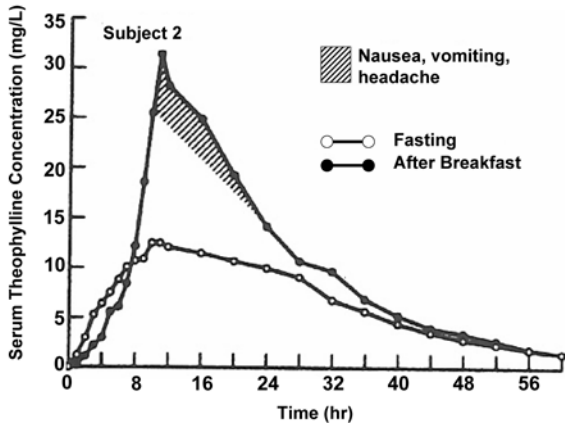

Figure 2. Theophylline serum concentrations in one volunteer who received a single dose of Theo-24 (UCB, Pharma, Inc, Smyrna, GA) fasting and with food on two separate study days. The shaded area represents the time period when this subject had symptoms of theophylline toxicity after dose-dumping. Reproduced with permission from *Chest*.[14]

variation of absorption of theophylline in children, Smolensky et al. discovered that a single dose of Theo-24 given on an empty stomach at bedtime produced much higher, and sometimes toxic, concentrations during the night than when the same dose was given in the morning, probably because of a higher pH in the small intestine during the night.[15]

Surprisingly, Theo-24 is one of the few slow-release theophylline products still available in the United States. Although there is a precaution in the labeling about taking this product fasting, most prescribers and pharmacists are unaware of this and fail to warn patients. Fortunately, slow-release theophylline is rarely prescribed; hence, few patients are exposed to this potential danger.

NON-PRESCRIPTION METAPROTERENOL INHALER

In 1982, FDA announced its intention to allow metaproterenol metered-dose inhaler (MDI) (Alupent) to be sold without a prescription. This change was made without consultation of its Pulmonary Allergy Drugs Advisory Committee or physician groups that specialized in the care of asthma patients. The FDA's rationale was that the existing epinephrine MDI (Primatene Mist; Wyeth Pharmaceuticals, Madison, NJ) was much less effective and potentially more toxic than metaproterenol. However, in FDA's review of the literature, they neglected to realize that in some countries, such as Australia, the generic name for metaproterenol was orciprenaline and that there were reports of increased deaths from asthma in patients taking this drug without prescription.[16] Our major concern was not toxicity from the drug but the fact that patients would have access to this drug without medical supervision and would continue to use it as asthma worsens, which would delay them from seeking medical care and initiation of systemic corticosteroids. Consequently, I led a campaign to get FDA to reverse their position on this issue. After failure to convince the then Chief of the Pulmonary Division that a mistake had been made, I enlisted the help of physician and pharmacy organizations to oppose this move. We also stimulated articles in the *New York Times*, *Washington Post*, and a story on ABC National Evening News Program. In addition, we brought this issue to the attention of Congressman John Dingle, who announced that he would conduct a congressional hearing on FDA's action. The Agency then hurriedly convened their Pulmonary Allergy Drugs Advisory Committee who voted to support our position, and subsequently FDA returned metaproterenol to prescription only status.

Before embarking upon this campaign, I gained the approval of the Dean of the College of Pharmacy and the Vice President for Health Affairs at the University of Florida. It was, indeed, fortunate that I had the foresight to do this since Boehringer Ingelheim, the manufacturer of Alupent, flew their Chief Executive Officer on a private jet to Gainesville to meet with the President of the University of Florida in an attempt to suppress my campaign. The President resisted the pressure from the company and I was allowed to continue my efforts.

MONITORING AMINOGLYCOSIDES IN CHILDREN

In 1980 when I moved from the University of Iowa to the University of Florida, I established a pharmacokinetic consultation service in collaboration with Allen Neims, MD, PhD, then Chairman of the Pharmacology Department. As part of this service, we were consulted to es-

tablish initial dosing, set up phlebotomy service to draw samples at appropriate times, and then use the results from the clinical laboratory to make written dosing recommendations in the patient's medical record.

At the time, it was conventional to obtain peaks and troughs in all patients receiving aminoglycosides. Dr. Ken Massey, who was completing a post-PharmD fellowship, noted that a large number of patients had therapeutic peaks and troughs. We subsequently analyzed the consultations for a three-year period and were able to determine that peaks and troughs were in the therapeutic range for all children over 1 year of age who had normal renal function, were treated for no more than 10 days with 2.5 mg/kg of gentamicin or tobramycin every 8 hours and were not being treated for pulmonary infections, which required higher peak concentrations.

The publication of our findings in the *Journal of Pediatrics* stirred some controversy, especially among PharmDs who were providing pharmacokinetic monitoring at other institutions.[17] However, over the ensuing years, our recommendations have been adapted, and monitoring aminoglycoside serum concentrations has become more selective.

PANCREATIC ENZYMES

Ninety percent of patients with cystic fibrosis (CF) have pancreatic enzyme insufficiency and require exogenous pancreatic enzymes to improve fat absorption. Because pancreatic enzymes were available before passage of the 1938 Pure Food and Drug Act, it has been legal for drug companies to manufacture and sell these products without FDA approval. Throughout the 1980s, microencapsulated formations such as Pancrease (McNeil Pharmaceutical, Fort Washington, PA) were the most frequently prescribed formulations for CF patients because the coating on the beads resisted acid inactivation in the stomach releasing enzyme in the small intestine and, therefore, improving fat absorption compared to conventional rapid release products.[18]

In 1989, a clinical nutritionist in the Pediatric Pulmonary Clinic at the University of Florida told me about one of our young adult patients who had been well-controlled on Pancrease but developed more frequent stools that were foul smelling after his pharmacist substituted a generic enzyme product that had just become available. A week later, a second patient called her, and Dr. Weinberger at the University of Iowa encountered a third patient. We collected the generic products from these patients, which were all manufactured by Anabolic, Inc., and distributed by different suppliers. We sent the enzymes to a commercial testing laboratory to evaluate the lipase activity in cold water and after one hour exposure to simulated gastric fluid (HCl at pH 1). We discovered that there was considerable variation in the enzyme content that did not correspond to the labeled amount and that after all three products were exposed to simulated gastric fluid, lipase was totally inactivated in one hour (Figure 3).[19] In contrast, Pancrease, which also contained nearly twice the amount of lipase as labeled, retained lipase activity after exposure to simulated gastric fluid. After we reported these results to FDA, the product manufactured by Anabolic, Inc. was withdrawn from the market.

Subsequently, pharmaceutics colleague Guenther Hochhaus, PhD, and a PharmD stu-

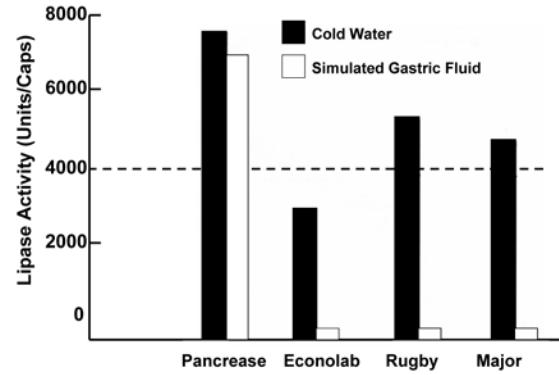

Figure 3. Lipase activity of Pancrease (McNeil Pharmaceutical, Fort Washington, PA) and a generic product from three patients with cystic fibrosis who experienced treatment failure. All three patients took a generic product manufactured by Anaholic, Inc. sold by three different distributors. Lipase from the generic product was totally inactivated when exposed to simulated gastric fluid *in-vitro* for one hour, whereas the brand name product (Pancrease) retained lipase activity.[19] Originally published in Hendeles L, Hochhaus G, Kazerounian S. Generic and alternative brand-name pharmaceutical equivalents: select with caution. *Am J Hosp Pharm* 1993;50:323-9 © 1993, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission. (R0810).

dent set up the lipase assay in the College of Pharmacy at the University of Florida and we evaluated all of the products on the market. We found that there were vast differences in the enzyme content compared to what was labeled, there were large between-product variations in the pH at which they released enzyme and there were vast differences in the amount of lipase activity after exposure to simulated gastric fluid.[20]

We presented the results of our *in vitro* studies of all products on the market in 1994 to the FDA urging them to regulate this group of drugs.[20] As a result of changes in the Directors of the Gastrointestinal Division at FDA, this issue came to the forefront and then fell between the cracks several times. In 2006 (12 years after our initial report of treatment failures) the FDA finally declared these products as new drugs and required new drug applications from manufacturers if they were to remain on the market after April of 2008. Interestingly, the apparent stimuli that led FDA to finally take this action were reports of adverse consequences of substituting newer generic products reported to the Cystic Fibrosis Foundation and pressure from Congressman Henry Waxman.

Because of difficulties in achieving the FDA requirement that the enzyme product contains the labeled amount, the Agency has extended the deadline to 2009 for companies who have already submitted a new drug application (Creon, Ultrase, and a new product from Eurand). To the best of my knowledge, neither McNeil, the manufacturer of Pancrease MT, nor the generic manufacturers have submitted a new drug application, so it is expected that they will not be able to sell their products after April 2008.

DELIVERY OF ALBUTEROL BY MDI AND HOLDING CHAMBER

For decades inhaled albuterol has been delivered by nebulizer in the treatment of acute asthma in hospitalized patients. In 1992 I collaborated with a physician in our emergency department who had a special interest in the management of asthma. We conducted a double-blind, randomized, parallel study comparing the effect of albuterol, 2.5 mg delivered by nebulizer, and 4 puffs (0.360 mg) from a MDI delivered through a valved holding chamber (VHC), every 30 minutes for up to six treatments in patients with acute asthma treated in the emergency department.[21] The results of this study indicated that FEV_1 improved equally well with both treatments, and all but two patients (one in each group) were able to obtain sufficient symptom relief to be discharged from the emergency department (Figure 4). Subsequently, there were a number of studies in children of all age groups, as well as in adults, indicating that there was no advantage to using the nebulizer.[22] Delivery by MDI+VHC is faster, requires less respiratory therapists' time, is more convenient and less expensive. However, there is often a great deal of resistance because of the mistaken belief by healthcare providers and patients that nebulizer therapy is more effective. In fact, a systematic review of the literature with meta-analysis of studies conducted in children less than 5 years of age indicated that the rate of hospital admission from the emergency department was significantly lower in children treated with the MDI+VHC attached to a

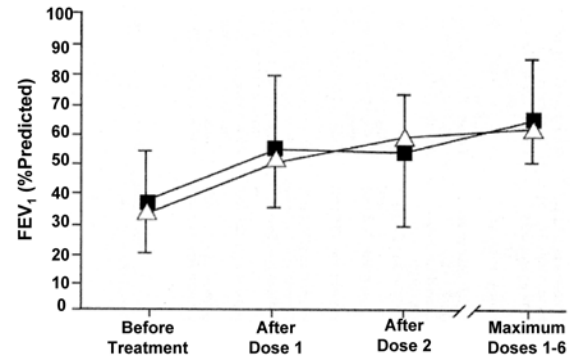

Figure 4. Forced expiratory volume in 1 second (FEV_1) in 35 patients with acute asthma treated in an emergency department in a randomized, double-blind, double-dummy, parallel manner with either 2.5 mg albuterol delivered by nebulizer (■) or 4 puffs of albuterol metered-dose inhaler delivered through an InspirEase (□) (Key Pharmaceuticals, Kenilworth, NJ) valved holding chamber every 30 minutes until symptom-free. There was no significant difference in response to albuterol delivered by the two different methods.[21] Originally published in Hendeles L, Hatton RC, Coons TJ, Carlson L. Automatic replacement of albuterol nebulizer therapy by metered-dose inhaler and valved holding chamber. *Am J Health-Syst Pharm* 2005;62:1053-61

mask compared to nebulizer and that the heart rate was significantly lower in the MDI+VHC-treated group.[23] It is important to note that the dose of the MDI has to be increased in order to achieve an equal therapeutic effect. In the various studies conducted, between 4 and 10 puffs of the MDI have been administered compared to the 2.5 mg of the nebulizer solution.[22]

DETERMINING ADHERENCE TO ASTHMA MEDICATIONS BY TELEPHONING THE PATIENT'S PHARMACY

It is well known that patients with asthma have poor adherence to their maintenance medication. As a clinical pharmacist in the Pediatric Pulmonary Clinic who interviews returning patients to determine how and when they use medication at home and whether they have adequate technique with inhalers, I realized that there was a discrepancy between what parents told us they did and the child's asthma control. We suspected that poor adherence was a frequent cause of treatment failure, but it was difficult to document this. I came up with the idea of telephoning the patient's pharmacy to obtain the prescription refill history as a method of measuring adherence. In collaboration with James Sherman, MD, a pediatric pulmonologist, we conducted a study in which 116 patients who presented to the Pediatric Pulmonary Clinic for a return visit were asked where they obtained their medication. We included only Medicaid patients in the study since we had the ability to confirm with the State Medicaid Office their reimbursement to pharmacies as a method of validating information provided by pharmacists. We also excluded patients who had received free samples from our clinic or other physicians. While each patient was being seen by Dr. Sherman, my students and I contacted the pharmacy and obtained the prescription refill history. During the clinic visit, Dr. Sherman rated on a checklist his assessment of adherence as either being greater than 80%, 50% to 80%, or less than 50% based upon his interview with the patient. The results indicated that Dr. Sherman's assessment greatly overestimated adherence, as measured by refill history, for maintenance medications such as inhaled corticosteroids.[24] In fact, his assessments were 50% correct, about the same as if he had flipped a coin. It is noteworthy that 92% of the responses from pharmacies were accurate when compared to reimbursement records from the Medicaid Office. We concluded that telephoning the patient's pharmacy was an effective method of detecting poor adherence to maintenance medications. If a one-month supply of medication was refilled once every three months, for example, the patient could not possibly be adherent. In a subsequent study, we found that our patients took only 44% of doses of inhaled fluticasone prescribed compared to 68% for oral montelukast.[25]

This method of assessing adherence is now routinely used by the physicians in our clinic and it often prevents prescribing additional drugs or performing invasive diagnostic procedures such as bronchoscopies in patients who fail to respond to therapy when it is discovered that they are poorly adherent. In these instances, intervention is focused on improving adherence.[26]

STUDYING BRONCHODILATORS DURING NOCTURNAL ASTHMA ATTACKS

It has been well recognized that the dose-response of short-acting β_2-selective agonists is relatively flat during the daytime. However, bronchodilators generally are evaluated in patients with an FEV_1 in the range of 60%-80% predicted. If, in fact, the dose-response curve is relatively flat, a new product or delivery method of the same drug could deliver 50% more or 50% less drug and not be detected by a difference in FEV_1. We, therefore, hypothesized that studying the dose-response during a nocturnal asthma attack would be more relevant since these patients have severe bronchospasm upon awakening with asthma which is reversible with bronchodilator. In fact, they experience this at home and treat themselves and go back to sleep. We recruited 16 patients with a history of nocturnal asthma attacks and randomly studied their response to albuterol during the daytime when they were asymptomatic and after waking with acute asthma while sleeping in the Clinical Research Center at the University of Florida. The results of the study indicated that FEV_1 was extremely low in the patients upon waking at night with

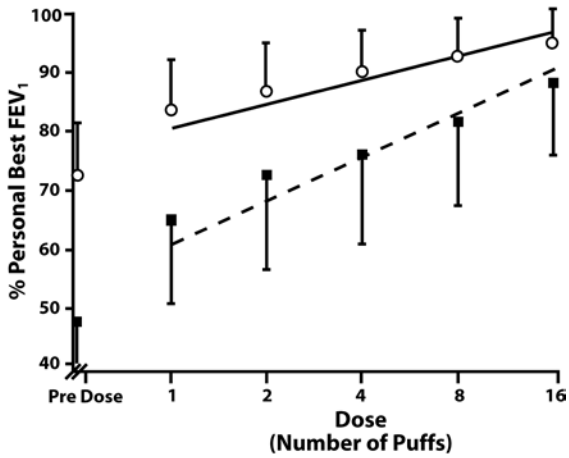

Figure 5. Forced expiratory volume in 1 second (FEV_1) in 15 subjects with asthma before and after doubling cumulative doses of albuterol metered-dose inhaler delivered through an InspirEase (Key Pharmaceuticals, Kenilworth, NJ) in randomized order during a nocturnal asthma attack (■) and during the day (□) when subjects were asymptomatic. The slope of the dose-response curve was significantly steeper during the nocturnal attack. The median dose required to achieve an FEV_1 of 80% was 5 puffs during the night and 0.4 puffs during the day.[27] Reprinted from the *Journal of Allergy and Clinical Immunology*, Vol. 117, Hendeles L, Beaty R, Ahrens R, Stevens G, Harman EM, Response to inhaled albuterol during nocturnal asthma, 773, ©2006 with permission from Elsevier.

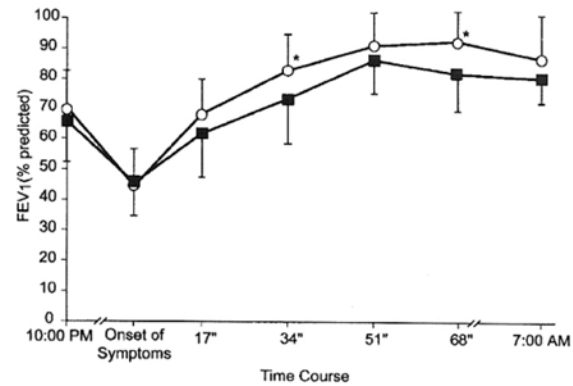

Figure 6. Forced expiratory volume in 1 second (FEV_1) in 8 subjects with asthma during a nocturnal asthma attack. Subjects were treated with doubling doses at 15-minute intervals with albuterol metered-dose inhaler (MDI) (□) or epinephrine MDI (Primatene Mist, Wyeth Pharmaceuticals, Madison, NJ) (■) in a randomized, crossover manner. FEV_1 was significantly higher after albuterol at 34 and 68 minutes but the differences were not clinically relevant. Reproduced with permission from *Annals of Allergy, Asthma, and Immunology*.[28]

symptoms, on average 44%, but with repeated doses (up to a cumulative dose of 16 puffs) FEV_1 increased to 84%. In contrast, the FEV_1 was 68% at baseline during the daytime and increased to 90%, a flatter dose-response curve (Figure 5).[27] During the night, a median of 5 puffs were required to reach an FEV_1 of 80%, whereas only 0.4 puffs were required during the day to reach this same clinically relevant endpoint. These results indicated that differences in the amount delivered to the airways would more likely be detected during nocturnal asthma than during the day and would provide a more relevant method of detecting a difference between two different β_2–agonists, or the same drug delivered by two different devices.

We subsequently studied in a randomized, unblinded, crossover design the response to albuterol and non-prescription epinephrine (Primatene Mist; Wyeth Pharmaceuticals, Madison, New Jersey) in eight patients with documented nocturnal asthma while sleeping in our Clinical Research Center.[28] It is noteworthy that with this small sample size, we were able to detect statistically significant, but not clinically relevant, differences in bronchodilator response at 34 and 68 minutes (Figure 6). Epinephrine was somewhat less effective than albuterol; it required almost twice as many puffs for the same effect. In contrast, the heart rate increased when patients were treated with albuterol, but decreased when they were treated with epinephrine (Figure 7). Most healthcare professionals have the bias that epinephrine is less safe than albuterol. However, the results of our study suggest that it is not bioavailable from the lungs when administered by the chlorofluorocarbons (CFC) MDI. That is, epinephrine has an alpha-adrenergic-receptor simulating effect which decreases transmucosal absorption. That is why dentists add it to local anesthetics to prolong their duration of action. Additionally, it is metabolized by catechol-o-methyl transferase in the lungs which inactivates it, and any drug that does reach the systemic circulation is rapidly metabolized by monoamine oxidase.

LUNG BIOAVAILABILITY OF INHALED CORTICOSTEROIDS IN YOUNG CHILDREN

The FDA approves spacer devices based

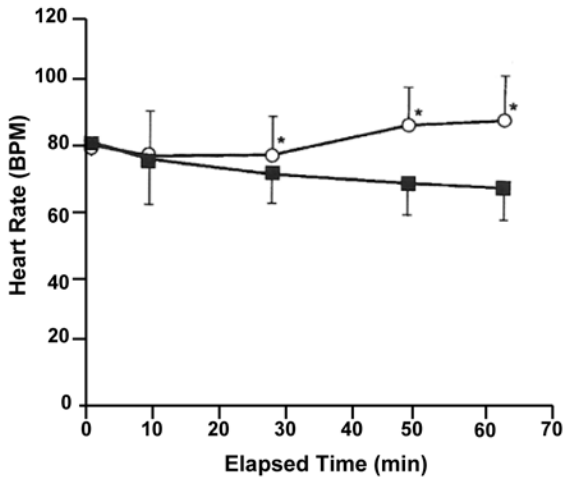

Figure 7. Heart rate in 8 subjects treated with albuterol (□) and epinephrine (■) metered-dose inhalers in random order during a nocturnal asthma attack (see Figure 6 for details). Heart rate was significantly greater during albuterol after the second dose (6 cumulative puffs). Reproduced with permission from *Annals of Allergy, Asthma, and Immunology.*[28]

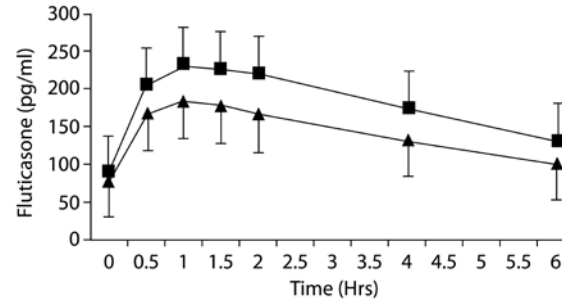

Figure 8. Steady-state fluticasone propionate plasma concentrations in 8 children with asthma (5-9 yr) after treatment with fluticasone metered-dose inhaler, 220 g twice daily, delivered through an InspirEase (Key Pharmaceuticals, Kenilworth, NJ) (■) and E-Z Spacer (We Pharmaceuticals, Ramona, CA) (■) in a double-blind, randomized order. The peak was 18% greater and the AUC 22% greater after InspirEase compared to E-Z Spacer. Adapted from Liang, et al.[29]

upon *in vitro* studies. However, there are very little *in vivo* data that differences between devices result in different amounts of drug being delivered to the airways. We, therefore, hypothesized that measuring fluticasone propionate serum concentrations would be a good marker of lung bioavailability in children. When patients inhale medications as much as 90% of the dose is swallowed. Since 99% of the swallowed dose of fluticasone propionate is inactivated by first-pass metabolism, drug in the blood exclusively is a result of absorption from the airways.

We first conducted a double-blind, randomized, crossover design study in 8 children (5-9 years of age) with asthma who inhaled fluticasone (CFC MDI, 220 μg twice a day for at least 2 days through the InspirEase (Key Pharmaceuticals, Miami, FL) valved holding chamber, and a generic equivalent for this device, the E-Z Spacer.[29] We measured steady state fluticasone concentrations over 6 hours. The results of this study indicated that InspirEase delivered 22% more drug than the E-Z Spacer (Figure 8). In addition, the one-hour concentration strongly correlated with the 6-hour area under the curve. This opened up the possibility that a single blood sample collected at one hour could be used to evaluate differences in drug delivery in young children who would not tolerate multiple blood sampling.

Using this methodology, we subsequently evaluated the delivery of inhaled fluticasone in preschool children using a conventional valved holding chamber with mask (AeroChamber Plus; Forest Pharmaceuticals, St. Louis, MO) and an anti-static device with mask (AeroChamber Max; Monaghan Medical Corporation, Plattsburgh, NY).[30] Twelve children (1-6 years of age) were treated with 2 puffs of 110 μg/puff CFC formulation (Flovent, GlaxoSmithKline, Research Triangle Park, NC) for a minimum of 3 days. A single one-hour post-dose plasma concentration was obtained after each treatment in a randomized, unblinded, crossover design. The results indicated that in five of the patients, the anti-static device resulted in a much greater deposition of fluticasone in the airways, but in seven children there was no difference (Figure 9). Thus, using an anti-static device had a variable effect. Since we regrettably did not measure the static charge with the device before obtaining the blood samples, the reason for the inconsistent effect was unknown. We speculated that the buildup of fluticasone in the patients who did not show a difference actually reduced the static charge, resulting in no difference between the devices in these patients.

Nevertheless, the results of this study indicate that this design is a useful way of measuring differences in delivery devices with only one venipuncture per treatment. We subsequently

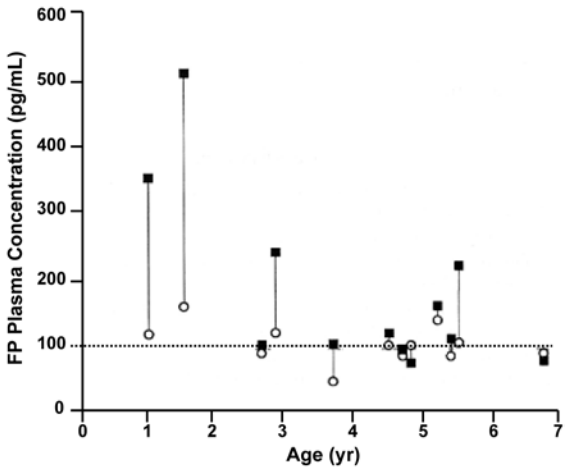

Figure 9. The one-hour steady-state fluticasone propionate plasma concentrations in 12 children (1-6 yr) treated with fluticasone metered-dose inhaler, 220 µg twice daily, delivered in randomized order by conventional (□) and anti-static (■) valved holding chambers with attached mask. Plasma concentrations were more than two-fold greater in 5 children after the anti-static chamber but there was no difference between the devices in 7 children.[30] This article was published in the *Journal of Pediatrics*, Vol. 149, Khan Y, Tang Y, Hochhaus G, Shuster J, Spencer T, Chesrown S, Hendeles L, Lung bioavailability of hydrofluoroalkane fluticasone in young children when delivered by an anti-static chamber/mask, 793-7, Copyright Elsevier 2006.

measured the one-hour steady state fluticasone plasma concentration in 60 children of different ages treated with different devices.[31] We found that the plasma concentrations in children who could effectively inhale the drug from the actuator alone without an assist device were significantly lower than in all children who used either a valved holding chamber with mouthpiece or mask, including 12 patients less than 5 years of age. Interestingly, the mean concentration in the youngest children who passively breathed through the device was not significantly lower than the mean concentration in children who could inhale deeply and hold their breath. This indicated that drug was effectively delivered to the young children, a concern of many clinicians. Thus, we concluded that use of a valved holding chamber actually increases lung bioavailability because less drug is swallowed and inactivated and more drug is available to be absorbed from the lungs. Additionally, the results indicated that delivering an inhaled steroid to young children through an MDI+VHC with mask was an effective method of delivery.

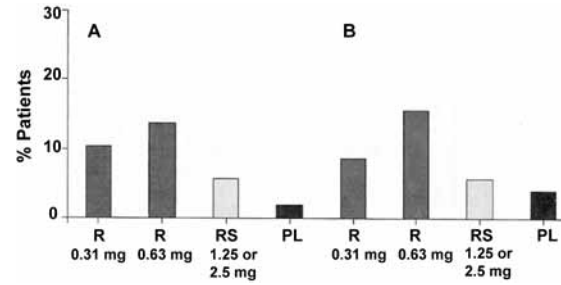

Figure 10. The frequency of asthma exacerbations (A) and adverse events requiring patient withdrawal from the study (B) in 211 children 2-4 yr treated with placebo (PL), 0.31 or 0.63 mg of levalbuterol (R), or 1.25 or 2.5 mg of racemic albuterol (RS) three times a day after three weeks in a double-blind, randomized, parallel study. Although the differences were not statistically significant, the Food and Drug Administration denied approval for levalbuterol for this age group based on this study. Adapted from reference 38. Originally published in Hendeles L, Hatton RC, Coons TJ, Carlson L. Automatic replacement of albuterol nebulizer therapy by metered-dose inhaler and valved holding chamber. *Am J Health-Syst Pharm* 2005;62:1053-61 ©2005, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission. (R0813).

LEVALBUTEROL NEBULIZER SOLUTION

In 1999, Sepracor Inc. obtained approval to market levalbuterol (Xopenex, Sepracor Inc. Marlborough, MA), the R-albuterol isomer, as a nebulizer solution. The marketing strategy for this product has been that it is more effective and causes fewer side effects than racemic albuterol. My colleague, Dr. Mike Asmus, and I evaluated all of the literature available at that time and concluded that levalbuterol was neither more effective nor safer, just much more costly.[32] In spite of the spin that the company put on subsequent publications, evaluation of the data in each of these studies clearly confirms our initial conclusion.[33-37] This is especially true in pediatric studies. In fact, FDA denied approval of levalbuterol for children 2-5 years of age based on a Sepracor Inc. study demonstrating numerically greater asthma exacerbations and adverse effects compared to racemic albuterol and placebo (Figure 10).[38]

It is noteworthy that to this day, I still receive emails from pharmacists across the country attempting to resist addition of levalbuterol to their hospital formularies. Publishing such reviews and letters to the editor is one way that I have been able to advocate for patients.

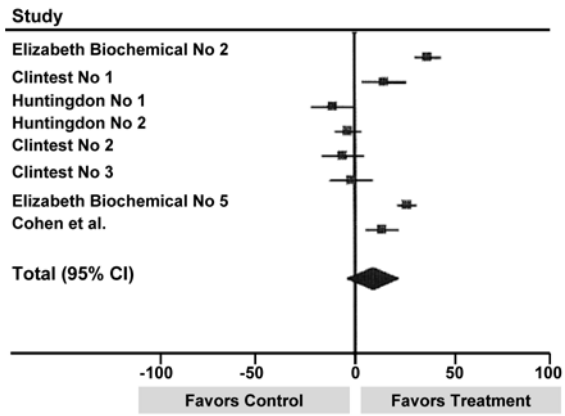

Figure 11. Funnel plot of 8 studies of oral phenylephrine 10 mg versus placebo reporting the mean maximum difference in decreases in nasal airway resistance over 120 minutes. The study is identified by the commercial testing lab that performed the study. The mean difference of 10% between phenylephrine and placebo was not statistically significant. Reproduced with permission from *Annals of Pharmacotherapy*.[42]

ORAL PHENYLEPHRINE AS A DECONGESTANT

In the 1970s, FDA issued a monograph on over-the-counter decongestants indicating that phenylpropanolamine, pseudoephedrine, and phenylephrine were effective and safe when given orally. Phenylpropanolamine was removed from the market in 2001 because of an association with hemorrhagic strokes. Pseudoephedrine has been moved behind the counter as a result of an amendment to the Patriot Act attempting to restrict access to pseudoephedrine which can be used to illegally make methamphetamine. As a consequence, manufacturers of brand name pseudoephedrine products have reformulated their products with phenylephrine at a 10 mg dose in order to avoid loss of sales in convenience stores, grocery stores, airports, etc., where there is no pharmacy.

However, the 10 mg maximum FDA approved dose is no more effective than placebo.[39] Because of high first-pass metabolism, phenylephrine has low oral bioavailability.[40] In contrast, topical phenylephrine nasal solution is highly effective at relieving nasal congestion.[41] Subsequently, my colleague Dr. Randy Hatton and I obtained through the Freedom of Information Act the studies upon which the FDA panel in the 1970s based their conclusion that phenylephrine was safe and effective. We conducted a systematic analysis of the literature with meta-analysis and concluded that the 10 mg dose was not significantly more effective than placebo (Figure 11).[42] Also, we filed a Citizen's Petition and in December, 2007, FDA convened their non-prescription Drugs Advisory Committee to discuss our petition. FDA was able to present a total of 14 studies, 7 of which showed no difference between placebo and 7 that showed a statistically significant difference in nasal decongestant effect. The Advisory Committee, as had the Panel in the 1970s, disregarded the 7 studies that showed no difference and concluded that there was some evidence of a difference at 10 mg but recommended that larger doses be studied. Interestingly, two recent well-designed pharmacodynamic studies conducted by Schering-Plough Corporation failed to demonstrate a significant decongestant effect of oral phenylephrine in environmental allergen chamber studies.[43,44] However, the Panel dismissed the results of these studies on the basis that they were not efficacy studies in patients with naturally acquired nasal stuffiness. The results of this Committee probably will mean that the FDA will continue to allow the 10 mg dose. Whether the Agency has the ability to stimulate manufacturers to conduct modern day studies at larger doses is debatable.

CONCLUSION

In the past 35 years I have had the good fortune to become a clinical researcher without formal training. I owe much of my success to Dr. Weinberger, who mentored me for five years and continues to be a valuable sounding board.

Throughout my career, I have maintained a clinical practice—now only two half days per week in the Pediatric Pulmonary Clinic at University of Florida. It is this continued clinical experience that has raised questions for me and my collaborators to research and in turn, the results of our studies have been applied to patient care. I have also had the opportunity to act as a patient advocate to the FDA on issues such as non-prescription metaproterenol, pancreatic enzymes, and over-the-counter oral phenylephrine.

DISCLOSURE Dr. Hendeles is a consultant to CompleWare Corporation, Merck and Co., Inc. and Xhale Diagnostics. He is on the Speaker's Bureau for AstraZeneca, Genentech/Novartis and GlaxoSmithKline and is on the Advisory Board for Merck and Co., Inc. He also has grant support from Altus Pharmaceuticals, Genentech and Ivax Research LLC.

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