Wheeze & Sneeze

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Simple, Safe, Effective, Cheap

Engineering solutions, one patient at a time

After 30 years of board certification and 20 years of serving your patients in South Jersey, I tried to define what keeps it exciting to go to work every day when many of my contemporaries are cutting down and backing out. I think the answer is the opportunity to learn from the patients we share, and use what they teach me to develop better ways to improve their health and that of others in keeping with the guidelines of ***simple, safe, effective*** and ***cheap***.

If we've seen enough of your patients, you've probably seen some of our tricks. These include: **hypertonic alkaline saline** mixed at home according to our recipes for nasal and sinus irrigation and as a nose spray; selective addition of topically acting steroids and antimicrobials for **sinus irrigation** to reduce need for systemic dosing with drugs of the same classes; **elevation of the head of the bed** to control laryngopharyngeal acid reflux; teaching not just to buy dust-proof mattress covers but **specific washing techniques** to kill dust mites; and also effective strategies to **reduce mite exposure** in areas other than the bed.

We manage the irritant component of allergic rhinitis with conjuncival lubricants of viscosity appropriate to the needs of the individual patient and we make eczema and a broad range of other inflammatory and hyperkeratotic skin conditions easier to live with and control with ***simple, safe, effective*** and ***cheap*** skin softeners and moisture sealants. For $25 per oz. you can buy products that both moisturize and seal dry skin. But if you seal when the skin is already wet, as in the shower or when wet from washing your hands, you can buy very effective moisture sealants for less than $5 per lb. On occasions, using **common sense** methodology, we've even been able to provide patients with enough feedback about cause and effect that they've actually implemented serious weight loss or stopped smoking.

Engineering solutions for diseases

Sometimes the light bulb goes on about a strategy that isn't cost-effective to implement for the individual patient but could significantly reduce the impact of disease. I'd like to share one of these projects even though it still hasn't been funded, as it illustrates the approach we take to every one of your patients.

You are probably familiar with the spring-loaded epinephrine injectors developed for self-treatment of anaphylactic

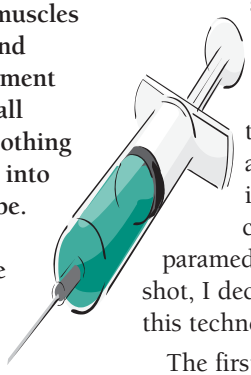
Continued on Page 2

Simple, Safe, Effective, Cheap

Continued from Page 1

reactions to foods, insect stings and sudden onset idiopathic anaphylaxis occurring outside of medically supervised settings.

Taking a paragraph to digress from the project to your practice, if you give allergy shots or potentially allergenic drugs in your office these devices costing $55-75 each are NOT the emergency dosage forms you want. Buy 1 ml epinephrine 1:1000 ampoules costing less than $2 each, dose .01 ml/Kg body wt up to a maximum dose of 0.5 ml, in syringes with needles long enough to reach through body fat into the muscles of the lateral thigh. Keep the epinephrine and syringe immediately available on your treatment area counter. Unless you're treating a football player with thigh pads, injecting through clothing beats delaying until you can get the patient into an examining room where he/she can disrobe. If the patient can take them by mouth also give rapidly acting H-1, H-2 and leukotriene receptor blockers but do not delay epinephrine while doing so. I discussed this in last year's *Wheeze 'n Sneeze*; if you need additional information please feel free to call our office.



Returning to the project, spring-loaded injectors have the drawbacks of being expensive, patients who have never or only rarely used them may not remember how and panic when they need them, and if they're startled by the jab and jerk the device out before the injection is complete, the epinephrine squirts onto the ground or the floor. The prospect of using these instruments of torture intimidates some patients who delay or do not use them at all for a condition for which treatment delay increases the risk of treatment failure. The needles on present devices are too short to reach thigh muscle in obese individuals and absorption from the more accessible deltoid is much slower than from the lateral thigh.

I had the honor of being chosen to give a "Highlights of the Annual Meeting" talk at the 2006 annual meeting of the American Academy of Allergy Asthma & Immunology, and my assigned range of topics included allergen immunotherapy. I thus had occasion to review in full detail a study of late systemic reactions to immunotherapy, 16% of which begin after usual post-allergy-shot office waiting times and which on occasion were still sufficiently severe to require emergency epinephrine. The authors recommended that all immunotherapy patients carry emergency meds for up to 6 hours after each shot. Another speaker reported animal studies with a rapidly disintegrating epinephrine tablet which when placed under the tongue at appropriate dose gave a timed blood level profile very similar to that of the Epi-Pen. When one of my own anaphylaxis patients refused to use her injector the first time she needed it, instead calling "911" and handing the device to the paramedics with the request that they give her the shot, I decided to see what I could do to help move this technology from the bench to the bedside.

The first step was to find a source of drug approved for human use. We discovered that a local compounding pharmacy can make it using technology that's already in the public domain, though the appropriate human dose is not known and without documentation of greater stability their shelf life is limited to 3 months.

Rapidly disintegrating sublingual tablets of isoproteranol + benzyl nicotinamide were used as asthma rescue medications in the 1950s, interestingly reported from Philadelphia and New Jersey. That literature does not document a safe and effective dosing range for sublingual epinephrine in humans. For safety we will have to begin with sublingual administration of the same 0.3 mg dose contained in the Epi-Pen and increase incrementally as tolerated in sequential challenges with continuous

Continued on Next Page

Continued from Previous Page

ECG and BP monitoring, as well as serial plasma epinephrine and serum potassium measurements. Our final target dose is 150% of the sublingual dose found to be equivalent to 0.3 mg of epinephrine by Epi-Pen in rabbits.

The South Jersey Regional Medical Center has experience with monitoring for acute adverse effects of injected medications in the conduct of clinical trials of cancer chemotherapeutic agents. It can schedule the monitored beds we need with one-on-one staffing by acute care nurses able to place IV lines and draw repeated blood samples. These beds are needed for patient care during winter respiration disease season, but available to us from April to October.

The funding issue is that the cost of an expected 60 hospital-based challenges and lab costs for sets of 12 serial plasma epinephrine levels per challenge push the total project cost to more than $100,000. This is above the funding limit of most research grant programs with rapid application turn-around times. The NIH is presently evaluating our application to determine whether we qualify for one of its grant programs with possible start dates between 7/07 and 7/08. There is also a private non-profit organization with a grant program for which this project is on target for both topic and dollar amount, with a probable start date of early 2008. We'd like to follow the initial adult study with a similar study in children, hopefully with a reduced number of challenges per patient. Funding delays may place us behind a pharmaceutical industry project to develop a similar product, though our rationale for requesting public sector funding whether sooner or later is that the technology we hope to validate is already in the public domain, and as such should enable health care cost savings of many times the cost of the study.

Validation of an inexpensive sublingual epinephrine dosage form is also timely, as medical interest groups in diverse specialties have made 2006 a year of both community and professional education in the recognition and management of anaphylaxis. We believe the availability of an inexpensive, generic, sublingual epinephrine tablet with validated dose equivalency will make a major contribution to compliance with treatment guidelines. We question the practicality, for example, of asking every allergy shot patient to carry a spring-loaded epinephrine injector for 6 hours after each allergy shot to cover the remote possibility of a late severe systemic reaction. We already ask such patients to carry rapidly acting oral mediator blockers, and we believe they would happily carry an emergency sublingual dosage form of epinephrine and use it appropriately if indicated.

Our compounding technique carries a 3 month shelf life in the absence of specific stability documentation, but we plan to measure both epinephrine content and dissolution rate of tablets from the same lots at age 1, 4, 7, 10 and 13 months. If we can establish stability of our formulation for 7 to 13 months, it will become economical for compounding pharmacies to prepare batches once or twice per year and accept prescriptions by the year, sending out present stock to fill each Rx and mailing replacement drug from the next lot before the original lot expires. A pharmaceutical industry formulation will require a longer shelf life to be commercially viable because of its longer distribution chain; though we believe the health and economy of the public will best be served if both their product and ours are available. The ability of any compounding pharmacist with a press for rapidly disintegrating tablets to make our formulation should put a lid on the price anyone can charge for a brand name version. However, a manufactured formulation on the shelf of your local pharmacy will be more readily available for those who need it immediately and those whose prescription insurance doesn't cover compounded products.

Continued on Page 4

Simple, Safe, Effective, Cheap

Continued from Page 3

Should your epinephrine-carrying patients volunteer to be subjects for this study?

The earliest study start date will be June 2007 or April 2008 depending on funding. However, some patients have already asked to get on our list, to have a sublingual dosage form as soon as possible. We only want study subjects who already have a medical indication to carry an emergency dosage form of epinephrine because we don't want to subject anyone to a challenge who doesn't have an indication to carry the same medication for possible use in an unmonitored setting. Study participants do not have to be AASJ patients and their participation in the study will not require that we become involved in their medical care.

The initial adult study will involve 10 patients age 18-45 who have clinical indications to carry emergency dosage forms of epinephrine. We have a diversity goal of at least 3 male, at least 3 female, at least 3 Caucasian and at least 3 non-Caucasian but may waive this if by doing so we can complete the study with a smaller number of lots of the short shelf life study drug. Female subjects cannot be pregnant or nursing and all subjects must be free of other diseases and conditions that could confound the study or predispose to adverse side effects. We hope to conduct a pediatric study beginning in 2009.

When choosing an allergist for your patients, remember that the allergist optimizes clinical outcomes by excellence as both an innovator and a teacher. In this issue I've shared some of what I do as an innovator. With regard to the teaching side of the equation, we'd like you to know that each of the two national allergy societies, the American Academy of Allergy Asthma and Immunology and the American College of Allergy Asthma and Immunology, has appointed me to the teaching faculty for it's current year program of continuing medical education for my fellow allergists.

We hope to pay study subjects $100 for each 3-1/2 hr. challenge session, and we will provide sublingual epinephrine for up to one year following the sudy if we have drugs within shelf life at a validated dose.

The first challenge for all study subjects will be an Epi-Pen administered according to package insert instructions. This will be followed at weekly intervals by increasing doses of sublingual epinephrine. The first two or three subjects will each receive 8 challenges as we'll have to start with the same dose given IM with the Epi-Pen. If we can confirm that blood levels only approach those of the Epi-Pen at sublingual doses in the same range found in rabbits, we will request IRB permission to start subsequent subjects at a higher dose and limit their total number of challenges to 4. We'd like to reduce the challenge number further for the pediatric study, to 3 and if possible 2 for the youngest children. Our ability to do this will depend on the variability we encounter in the dose response of adults.

Reference to animal study of equivalent doses of IM and sublingual epinephrine:
Rawas-Qalaji MM, Simons FER, Simons KJ: Sublingual epinephrine tablets versus intramuscular injection of epinephrine: Dose equivalence for potential treatment of anaphylaxis. J. Allerg. Clin. Immunol 2006(Feb); 117(2): 398-403.

Do you have colleagues who aren't on our mailing list and would like their own copies?

If so, ask them to contact us by phone (856.825.4100) fax (206.202.2105) or email (aasj@aasj.com) with their name, degree, medical specialty, mailing address, phone, fax and e-mail.

If you have patients who would like to participate in the sublingual epinephrine study, please either contact us by any of the above routes or ask the patients or parents to do so, themselves.