

786 Follow-Up Study on Latex Allergy in Health Care Workers

Cezary M Palczynski*, Jolanta M Walusiak*, Tomasz A Wittczak*, Urszula Ruta*, Pawel Gorski§ *Institute of Occupational Medicine, Lodz, Poland §Medical University of Lodz, Lodz, Poland

The analysis of natural history of allergy to a natural rubber latex (NRL) in health care workers, including the influence of exposure cessation on the clinical status and objective allergy markers was the objective of the study. The study covered 29 patients with recognised allergy to NRL, who were followed for 2 years after diagnosing NRL allergy. Following methods were used: physical examination, skin prick tests to common allergens and latex, determination of total serum IgE level and NRL - specific IgE antibodies, rest spirometry, histamine challenge test. Two years after the cessation of exposure to NRL, symptoms became less severe in the majority of patients and even a clearance of allergic symptoms was observed, as well as the decrease in doses of inhalative glucocorticosteroids was noted. This was accompanied by the decline in non-specific bronchial hyperactivity. Although the skin prick tests showed tendency to remain positive, the decrease in the level of specific IgE level was found in 17 subjects (including the RAST negativisation in one case). In conclusion, significant reduction of clinical symptoms or even total remission of allergic symptoms in NRL-sensitized subjects is often observed after exposure cessation.

787 Specific IgE Antibodies in Fatal Reactions to Hymenoptera Stings

Donald R Hoffman Brody School of Medicine at East Carolina University, Greenville, NC

Specific IgE testing to Hymenoptera venoms was performed on post-mortem sera from 51 victims of fatal insect sting anaphylaxis, 8 victims of fatal anaphylaxis to foods, 9 from drugs, 3 with fatal anaphylactoid reactions from drugs, and 31 control sera from rheumatology patients. Of the venom patients, 5 had fire ant reactions, 9 reactions were to bee and 37 to vespids. Negative ranges for each of the 6 venoms were determined from the 31 control sera. Two results to fire ant venom from the controls were not included in calculations because they were more than 5 times mean binding. Using the lowest cut-off point for positives at 0.22ng/ml, 5 (10%) of the sera from fatal venom reactions were negative. All of these victims had convincing witnessed histories. At 3 s.d. above mean control binding, 9 (18%) sera from fatal reactions were negative, and at 4 s.d., 13 (25.5%) were negative. At 3 s.d., 4 (13%) of the control sera and 6 (29%) of the food and drug sera were positive. Both groups were significantly different from the fatal venom reaction groups by chi squared and Fisher exact test. Receiver operating characteristic analysis of the results for venom fatalities against both other groups combined showed an area of 0.85 with an optimum point of 77% sensitivity and specificity at a cutoff of 3 s.d. above the mean binding of the control sera. At a cutoff of 2 s.d. sensitivity was 90% with a specificity of 65%. Of the 51 victims of fatal anaphylaxis, 5 had undetectable IgE antibodies, 12 (24%) had levels of specific IgE between 0.35 and 0.6ng/ml, and an additional 12 (24%) levels between 0.7 and 1.1ng/ml. These results support recent studies that indicated many patients who have recently experienced severe reactions to Hymenoptera stings, may have undetectable or low levels of specific IgE by intradermal skin testing and/or in vitro specific IgE testing. In this study 57% of the sera from patients with fatal anaphylactic reactions from stings had specific IgE ranging from undetectable to 1.1ng/ml. Very low amounts of venom specific IgE can be present in sera of victims of fatal anaphylactic reactions from stings.

788 Is Epinephrine Administration From a Sublingual Tablet Feasible for the Out-of-Hospital First Aid Treatment of Anaphylaxis? Absorption Studies in an Animal Model

X Gu, KJ Simons, F Estelle R Simons University of Manitoba, Winnipeg, MB, Canada

PURPOSE: Prompt administration of epinephrine, preferably by intramuscular (IM) injection (Simons et al, J Allergy Clin Immunol 1998;101:33-7) is the cornerstone of systemic anaphylaxis treatment. In the out-of-hospital first-aid treatment of anaphylaxis; however, patients may delay epinephrine self-injection due to fear of "a needle". It is not feasible to administer epinephrine orally because it is rapidly conjugated and oxidized in the gastrointestinal tract and liver by catechol-O-methyl-transferase and monoamine oxidase. In order to evaluate the rate and extent of sublingual absorption of epinephrine, we performed a prospective, randomized, four-way crossover study in a rabbit model.

METHODS: On 4 study days at least one week apart, six New Zealand white rabbits (4.2±0.1 kg) received either sublingual epinephrine tablets 2.5 mg or 10 mg, or epinephrine 0.03 mg IM (positive control), or 0.1 mL 0.9% saline IM (negative control). Blood samples were obtained at 0, 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, and 180 minutes after epinephrine administration. Plasma epinephrine concentrations were measured by HPLC with electrochemical detection. The assay was linear over a range of 25-1000 pg with a coefficient of variation of 3%. Pharmacokinetic and statistical analyses were performed using WinNonlin and PCSAS. Differences between peak plasma epinephrine concentrations (C_{max}) and time to peak plasma epinephrine concentrations (t_{max}) were considered to be significant at $p \leq 0.05$.

RESULTS: After epinephrine sublingual tablet 2.5 mg administration, the mean (\pm SEM) C_{max} was 2369.4±392.1 pg/mL, reached at a mean t_{max} of 20.8±5.7 minutes. After epinephrine sublingual tablet 10 mg administration, the C_{max} was 10835.8±2234.1 pg/mL, reached at a t_{max} of 21.7±5.4 minutes. After IM injection of epinephrine, the C_{max} was 6445.0±4233.4 pg/mL, reached at a t_{max} of 15.8±4.7 minutes. In the saline control study, the C_{max} (endogenous epinephrine) was 518.3±142.0 pg/mL. The t_{max} after both doses of sublingual epinephrine did not differ significantly from the t_{max} after IM epinephrine, and the C_{max} after the 10 mg sublingual epinephrine dose did not differ significantly from the C_{max} after IM epinephrine. No adverse effects were noted.

CONCLUSIONS: Sublingual tablet administration of epinephrine results in high, rapidly achieved peak epinephrine plasma concentrations similar to those achieved after IM injection of epinephrine. Absorption studies are now underway in humans to determine whether or not sublingual tablet administration of epinephrine will be a feasible alternative to self-injection of epinephrine in the out-of-hospital first-aid treatment of anaphylaxis.

789 Detection of Milk Proteins in Dry Powder Inhalers Containing Lactose

Anna H Nowak-Wegrzyn*, Ludmilla Bardina§, Kirsten Beyer¥, Wayne G Shreffler¥, Hugh A Sampson¥ *Mount Sinai School of Medicine, New York, NY §Mount Sinai School of Medicine, Jaffe Food Allergy Institute, New York, NY ¥Mount Sinai Medical Center, New York, NY

Patients with asthma and severe milk allergy frequently question whether dry powder inhalers (DPIs) containing lactose are safe for them because of the fear of milk contamination. DPIs product information inserts don't comment on the possibility of milk contamination and don't include contraindications for their use in milk-allergic individuals. To our knowledge, the issue of pharmaceutical grade lactose as a source of potential milk contamination has not been studied. We investigated DPIs that contain lactose as an ingredient to determine if milk protein is present. Lactose excipient in DPIs improves the efficiency of the blister pack emptying upon

breath activation, as well as drug delivery into the small airways. Over 98% of lactose settles in the oropharynx because of the large particle size (>50 µm) and is swallowed. The pharmaceutical grade lactose is obtained from skim milk. Acid-precipitated casein and heat-coagulated whey are removed by filtration. The presence of milk protein was determined by sensitive inhibition-ELISA assay, as previously described (Sampson et al, *JACI* 1991; 118:520-25). Briefly, DPI samples were extracted overnight. Standard curves were generated to whole milk, casein, and whey protein standards, range from 1 ng/ml to 30 µg/ml. Diluted samples and standards were pre-incubated with rabbit anti-milk IgG, and following washing and blocking, applied to the microwell plates. Peroxidase-labeled goat anti-rabbit IgG was added to the washed plates and developed. Absorbance was measured by ELISA reader. Samples from two different lots of each: Serevent™ Discus®, Advair™ Discus® (100/50, 250/50, 500/50), Flovent™ Rotadisc® (GlaxoSmithCline), and Foradil™ Aeroliser® (Novartis) were tested. Milk proteins were detected in all tested DPIs. Whey proteins were present at much higher concentrations than casein or whole milk protein, consistent with the method of lactose purification. Food allergen inhalation can induce acute bronchospasm in food allergic patients. In addition to local lung effect, systemic allergic reactions might result from milk protein absorption from lung mucous membranes or ingestion of swallowed lactose from DPIs. The threshold dose of inhaled milk protein for inducing an allergic reaction has not been established. However, children with severe milk allergy have been previously reported to experience acute allergic reactions following ingestion of food products containing >10 parts per million of total milk protein. Clinical challenge studies are necessary to determine significance of milk contamination in DPIs and to establish whether these medications can be safely used in milk-allergic patients with asthma.

790 FDA-Cleared Immunoassays for Latex-Specific IgE Are Missing Allergenic Epitopes From Multiple Hevb Allergens

Robert G Hamilton*, Raymond Biagini§, Barbara Mackenzie§, Hoong-Yeet Yeang¥, Siti Arijah¥, David I Bernstein€ *Johns Hopkins University School of Medicine, Baltimore, MD §NIOSH, Cincinnati, OH ¥Rubber Research Institute of Malaysia, Kuala Lumpur, Malaysia €University of Cincinnati, Cincinnati, OH

BACKGROUND: In the absence of an FDA-approved latex skin testing reagent, serological tests for latex-specific IgE have become essential confirmatory diagnostic tests. Two independent studies (*JACI* 103:925-30, 1999; *Annals AAI* 84:193-6, 2000) have shown diagnostic sensitivity of the most widely used blood tests (Pharmacia CAP System, DPC AlaSTAT) at 73-80% in comparison to puncture skin tests (PST), indicating a 20-27% false negative rate.

OBJECTIVE: To identify missing latex allergen specificities in the CAP and AlaSTAT reagents to target assay reagent improvement.

METHOD: Serum from 60 healthcare workers with a positive latex allergy history and positive PST using non-ammoniated latex [NAL] (*JACI* 98:872-83, 1996) were analyzed for IgE specific for latex (CAP, AlaSTAT) and purified native *Hevea brasiliensis* [Hevb] allergens 1, 2, 3, 4, 6.01, 7b, 7c and recombinant Hevb 5. The 8 Hevb-specific IgE immunoassays (EIA) were performed with purified allergen adsorbed onto microtiter plates. Each assay was calibrated with a human IgE anti-NP chimeric antibody dose-response curve and bound IgE was detected with biotin-monoclonal anti-human IgE Fc (clone HP6061) and peroxidase-streptavidin. Analytical sensitivity of all 8 IgE anti-Hevb EIAs was 0.5 ng/ml.

RESULTS: The diagnostic sensitivity displayed by the CAP (49%; 28+/57) and AlaSTAT (67%; 40+/60) for latex-specific IgE in serum as compared to PST was lower than previously reported. Of the 57 sera from Hx and PST positive subjects tested by EIA for Hevb-specific IgE, 12 CAP negative sera (21%) and 9 AlaSTAT negative sera (15%) contained no detectable IgE

antibody to any of the 8 individual Hevb allergens. Of these, interestingly, 11/12 (CAP) and 9/9 (AlaSTAT) specimens were from subjects who had positive PSTs to one or more of the 8 Hevb proteins, indicating the greater sensitivity of the PST. The remaining 17 CAP and 11 AlaSTAT negative sera (all from NAL PST positive subjects) fell into 3 positive IgE anti-Hevb patterns: Hevb 2-4-7b (n=9 CAP; n=7 AlaSTAT), Hevb 5 (n=6 CAP; n=2 AlaSTAT), Hevb 6 (n=2 CAP, n=2 AlaSTAT). CAP and AlaSTAT positive sera displayed heterogeneous IgE anti-Hevb patterns, with Hevb 5, 7b > 2, 4, 6 > 7c, 1, 3 being the IgE specificities in order of greatest frequency.

CONCLUSION: The suboptimal diagnostic sensitivity of two widely used commercial IgE anti-latex serology tests (CAP, AlaSTAT) has been confirmed with a new set of patients. Latex reagents in both assays appear to be missing immunoreactive allergenic epitopes from multiple latex allergens (Hevb 2, 4, 5, 6, 7b). Whether the absence of a complete Hev b allergen presentation in commercial diagnostic latex reagents results from poor handling of source latex or differences in the treatment of latex during reagent and glove manufacturing needs further investigation.

791 Risk Factors for Asthma Hospitalizations in a Managed Care Organization: Development of a Clinical Prediction Rule

Michael Schatz*, E Francis Cook§, Diana Petitti*, Anita Joshua* *Kaiser-Permanente, San Diego, CA §Harvard School of Public Health, Boston, MA

BACKGROUND: Asthma-induced hospitalizations are expensive in both economic and humanistic terms. Reliable identification of patients at higher risk for these outcomes would facilitate targeted intervention. The objective of this study was to use a computerized administrative database to develop and validate a clinical prediction rule for the occurrence of asthma hospitalizations.

METHODS: Subjects were asthmatic patients aged 3-64 continuously enrolled in Southern California Kaiser-Permanente in both 1998 and 1999. Outcomes and predictors were obtained from the Asthma Clinical Identification Database (ACID), based on linkage of computer data from a hospital discharge database, a diagnosis and procedures database, a membership database, and a prescription database. The outcome was any 1999 hospitalization with a primary diagnosis of asthma. Potential predictors included age, gender, zip code-derived median household income, San Diego or Los Angeles location, number of 1998 hospitalizations and emergency department visits, number of 1998 dispensings of anti-inflammatories, beta agonists and their ratio, number of 1998 oral corticosteroid dispensings, and number of 1998 prescribers.

RESULTS: The final case identification cohort included 4,197 children aged 3-17 and 6,904 adults aged 18-64. Univariate analyses showed that hospitalized children were younger than non-hospitalized children and less likely to have been from the San Diego medical center. Adults and children hospitalized in 1999 lived in zip codes with lower mean household income, were more likely to have required an emergency department visit or hospitalization in 1998, used more beta agonists and oral corticosteroids in 1998, and had more 1998 prescribers than non-hospitalized patients. In multivariable analysis, independent predictors of 1999 hospitalization in children included age and 1998 hospitalizations, beta agonist dispensings, total anti-inflammatory dispensings, and number of prescribers. Multivariable analysis in adults showed that 1998 hospitalizations and oral steroid dispensings and income were independent predictors of hospitalization in 1999. These final models were able to identify high risk groups of 11-13 % of the population who were at approximately a six-fold increased risk of experiencing a 1999 hospitalization and which included about 45 % of those subsequently hospitalized.

CONCLUSION: These models can be used to identify high-risk asthmatic patients in whom targeted intervention might reduce asthma morbidity and cost of care.