Lack of latex allergen contamination of solutions withdrawn from vials with natural rubber stoppers

DAVID J. THOMSEN AND TIM G. BURKE

Abstract: The effect on latex allergen contamination and microbial growth of a latex-allergy precaution technique for preparing injectable products was studied.

The study consisted of three parts: (1) preparation of 20 samples from vials with latex-containing stoppers in accordance with conventional guidelines, (2) preparation of 20 samples in accordance with latex-allergy precaution guidelines, and (3) preparation of 5 latex-free samples and 1 latex-contaminated sample as negative and positive controls, respectively. The conventional method involved swabbing a vial top with an alcohol prep pad, puncturing the dry natural rubber stopper with an 18-gauge needle attached to a latex-free syringe, and withdrawing the contents of the vial into the syringe. The latex-allergy precaution preparation technique was similar, except that the stopper was removed before the vial contents were withdrawn.

There was essentially no difference in latex allergen concentrations between the two drug preparation methods. None of the samples prepared with the standard method supported any microbial growth. One sample prepared with the latex-allergy precaution method grew bacteria.

Removal of the dry rubber stopper from vials did not yield solutions with less latex allergen than solutions prepared according to conventional guidelines.

Index terms: Allergies; Closures; Contamination; Drugs, adverse reactions; Injections; Latex; Sodium chloride; Vials

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Latex, or natural rubber, contains protein antigens that can cause an immediate hypersensitivity reaction.[1] These reactions have been elicited by exposure to latex-containing gloves, condoms, barium enema catheters, bladder catheters, balloons, rubber dental dams, toys, dental prophylaxis cups, and sports equipment.[2,3] Reactions to latex are mediated by immunoglobulin E (IgE) and manifest clinically as rhinitis, conjunctivitis, urticaria, bronchospasm, angioedema, and anaphylaxis.[4] Certain groups are at increased risk of developing latex allergies. Different people react to different amounts of latex allergen; highly sensitive individuals may have an acute reaction upon exposure to very small quantities. Well-defined risk groups include patients with neural tube defects or congenital urologic disorders who undergo frequent urologic, orthopedic, or neurosurgical procedures; health care workers; and other occupationally exposed workers.[1-3,5-16] Approximately 0.8% of the general population is latex sensitive.[16] Health care workers appear to have a 5–10% risk of latex allergy.[2] The group with the highest frequency (10–65%) is children with spina bifida.[17]

Risk factors for the development of latex allergy include frequent and early exposure to latex, the number of previous surgical procedures, and atopy.[4,9,11,13,15,18] Little can be done to limit necessary surgeries, and nothing can be done to change a history of atopy. Thus, identifying sensitive patients and avoidance of unnecessary exposure principally guide the management of latex allergy.[1,2,8,18] Health care workers are encouraged to follow specific guidelines and techniques to minimize exposure to latex.[3,6,8,11,15,16,19] General precautions that eliminate the use of powdered latex gloves, latex-containing catheters, and other latex-containing medical supplies may reduce or eliminate the risk of an allergic reaction in sensitive patients.[20-22] Latex-free medical products are not universally available, however.

It has been postulated, but not proven, that using medications from a multidose vial with a rubber stopper could deliver latex allergen to a susceptible patient.[23,24] There have been a few documented cases implicating vial stoppers as the cause of a reaction.[19,25,26] A special drug prepa-

DAVID J. THOMSEN is Clinical Pharmacist and TIM G. BURKE, PHARM.D., is Clinical Pharmacy Specialist, Department of Pharmaceutical Care, The University of Iowa Hospitals and Clinics, Iowa City.

Address reprint requests to Mr. Thomsen at the Department of Pharmaceutical Care, The University of Iowa Hospitals and Clinics, Iowa City, IA 52240, or to david-thomsen@uiowa.edu.

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ration technique, known as the latex-allergy precaution preparation method, has been developed at our institution for handling products with latex-containing vial stoppers when alternative, latex-free products are unavailable. This method is largely based on recommendations of the American Association of Nurse Anesthetists.[16] Although this preparation method may offer theoretical advantages to the patient, it has not been proven superior to standard drug preparation techniques in reducing latex exposure.[5] Also, since latex is water soluble, liquid medications packaged in vials with latex-containing stoppers could already have latex antigen in solution, so removing the vial stopper may not prevent latex exposure.[3] Therefore, latex-free products should be chosen whenever possible.

Our current medication preparation guidelines for latex-sensitive patients call for the physical removal of latex-containing stoppers in an effort to create "latex-minimized" doses for injection. The metal ring surrounding the vial stopper is taken off with a decapper or a hemostat, and the stopper is removed. The appropriate dose of medication is then withdrawn through the open vial top.

There is no evidence that this special preparation technique actually decreases the latex content of the injectable product.[5] Theoretically, there may be a higher chance of microbial and particulate contamination because of the increased manipulations used in preparation. The patient may be at higher risk of developing an infection from injected doses. This method may also place the health care worker preparing these products at risk of exposure to potentially harmful chemicals. Thus, certain products, such as antineoplastic agents, should not be prepared with latex-minimizing techniques. This may limit the treatment options available. In these situations, the physician is consulted and consideration is given to premedicating the patient, modifying procedures to maintain product integrity and hospital staff safety, or using alternative therapies.

We performed a study to compare our latex-allergy precaution preparation method with the standard method of preparing injectable products with respect to latex allergen contamination and microbial growth.

Methods

The study consisted of three parts: (1) preparation of 20 samples from vials with latex-containing stoppers in accordance with the conventional guidelines, (2) preparation of 20 samples in accordance with the latex-allergy precaution guidelines, and (3) preparation of 5 latex-free samples and 1 latex-contaminated sample as negative and positive controls, respectively. To protect the people performing the assay for latex, we used an inert substance, 0.9% sodium chloride injection, as our test solution.

A pharmacy department employee who is annually recertified in aseptic technique by the department (which runs an aseptic technique certification program) used 10-mL latex-free syringes[a] to prepare the samples in a laminar-airflow hood. In the first two parts of the study, the employee aseptically withdrew samples from vials with stoppers containing 13.4–16% natural rubber latex.[b] In following the conventional guidelines for preparing injectable drug products, the employee swabbed a vial top with an alcohol prep pad, punctured the vial stopper with an 18-gauge needle[c] attached to a latex-free syringe, and withdrew the contents of the vial into the syringe. Using the latex-allergy precaution preparation technique, the employee swabbed a vial stopper with an alcohol prep pad, removed the vial stopper with a decapper, and withdrew the vial contents through an 18-gauge needle attached to a latex-free syringe. To prepare the controls, the employee withdrew five 5-mL samples from the latex-free administration port of a 250-mL polyvinyl chloride bag of 0.9% sodium chloride injection[d] and one 5-mL sample of 0.9% sodium chloride injection that had been stored for 24 hours in a powdered latex glove. Samples were randomly numbered so that the laboratory personnel were blinded to the preparation method.

Each test sample was divided into two 5-mL volumes (stored in 10-mL latex-free syringes with plastic syringe tip caps[e]); one was sent to an outside laboratory[f] for latex allergen concentration determination, and the other was sent to our microbiology laboratory and incubated at 37 °C for 72 hours for microbial growth determination. The control samples were sent only for latex allergen testing. Latex allergen was measured with an inhibition immunoassay involving latex-specific human IgE, as described by Swanson et al.[27] The limit of detection of the immunoassay was 250 ng/mL.

Test results for the three study parts were compared for differences in latex allergen concentration (reported in nanograms per milliliter) or evidence of microbial growth. A sample (other than the positive control) was considered to be contaminated with latex allergen if the latex allergen concentration was greater than the assay's limit of detection.

Results

There was essentially no difference in latex allergen concentrations between the two drug preparation techniques. Seventeen of the 45 test samples and negative controls had 250–540 ng of latex allergen per milliliter. The amount of measurable allergen in these samples was about 0.1–0.2% of the allergen content extracted from powdered gloves in a similar manner (Swanson MC, Allergic Diseases Research Laboratory, Mayo Clinic, personal communication, 1997 Aug 8). The positive control had a latex allergen concentration of 231,000 ng/mL,

nearly 1000 times the limit of detection.

Upon reviewing the results, we questioned whether some of these samples were actually contaminated with latex allergen, because the results were close to the assay's limit of detection. To address this in a definitive manner, the laboratory pooled and lyophilized the 17 samples considered to be contaminated with latex allergen. The lyophilized powder was reconstituted with 0.1 M phosphate-buffered saline (pH 7.5) to a concentration 40 times higher than that of the original pool. This preparation also contained the original sodium chloride. A preparation of saturated sodium chloride solution was used as a control to evaluate ionic interference from the sodium chloride in the immunoassay. The results of this test indicated that no latex allergen was present. The original samples were at the detection limit because of the effect of sodium chloride binding to the antibodies in the assay; these original preparations at a 40-fold concentration would have demonstrated measurable allergen if it was present (Swanson MC, personal communication, 1997 Aug 8).

None of the samples prepared with the standard method supported any microbial growth. One sample prepared with the latex-allergy precaution method grew bacteria (a gram-positive coccus).

Discussion

Various manufacturing methods use natural rubber latex to make different types of products. Dry rubber syringe plungers, vial stoppers, and intravascular injection ports are examples of products compression molded or extruded from dry natural rubber, whereas latex gloves, catheters, and condoms are examples of products manufactured by dipping or coating with liquid natural rubber latex products. Dry rubber latex products have been reported to elicit allergic reactions less frequently than natural rubber products, and it appears that dipped latex products pose a higher risk than molded latex products.[14] Yunginger et al.[28] postulated that dry molded rubber products contain lower residual latex protein levels or that the proteins are less easily extracted. In support of this, Melton[29] studied the relative allergenicity of rubber stoppers from plastic syringes and found that these products have significantly less allergenicity than raw latex or latex surgical gloves. Thus, it seems that medication vial stoppers are not a major source of latex allergen. Caution must still be taken, because in certain highly sensitized patients even minute amounts of latex antigen may cause an allergic reaction.

Some authors and a professional nurse anesthetists' association suggest that latex-containing vial stoppers be removed before medication is withdrawn.[8,15,16,21] While it has been postulated that this practice reduces the potential for latex exposure, there are no studies to support this. An attempt to extract measurable latex protein from a vial stopper succeeded only after 40 needle punctures through the latex-containing stopper.[30] Some believe that medications with a latex-containing vial closure should be avoided altogether because latex is water soluble and the medication has already come in contact with the latex stopper.[3] Vassallo et al.[19] described a case in which the latex-containing vial stopper was removed and the patient still reacted. However, it was subsequently noted that the product the patient supposedly reacted to was from a supplier that did not use latex in any way in its manufacturing process.[31] Several other cases have implicated vial stoppers as a potential source of the reaction.[25,26] A more conservative approach is not to use medications stored under latex closures if a substitute is available in a non-latex-covered storage vial.[12] A filter has also been suggested for removing latex proteins, but this approach does not remove latex allergens.[3]

The main problem in developing latex-allergy precaution guidelines for products with vial stoppers is the lack of relevant data. Special preparation techniques may have inherent risks. For example, microbial and particulate contamination could increase patient morbidity and mortality and expose health care workers to potentially harmful chemicals. Also, special techniques may be cost-ineffective because of shortened expiration times and increased drug waste caused by the removal of vial stoppers. An effect on costs would be difficult to quantify, and our study was not designed to attempt it.

Our finding of no detectable difference in latex allergen concentrations between standard and latex-allergy precaution preparation methods supports our hypothesis that manipulation of the vial and removal of vial stoppers have no detectable effect on the amount of latex allergen in the medication. Although our sample was too small to allow any meaningful conclusions about sterility, this practice may increase microbial contamination of the products.

A limitation of this study was the sensitivity of the latex immunoassay. The inhibition immunoassay using specific human antibodies to IgE is sensitive to 250 ng of latex protein per milliliter of test solution. The study showed that there was no latex antigen in samples prepared by either method to the level of detection of the assay. We did not design the study to prove or disprove that these products are completely latex free, but to see if the latex-allergy precaution preparation technique offers a potential advantage over conventional methods of preparing injectable drugs. The small sample size precluded analysis for statistical significance.

Any potential benefit that might be achieved by removing the molded rubber stopper needs to be weighed against the potential dosage errors

(particularly in pediatric patients), dilution problems, contamination, and waste.[14] Our study suggests that a special latex-minimizing preparation technique for injectable medications offers no advantage over standard preparation methods. This study was not intended to evaluate other methods of avoiding latex, such as eliminating latex-containing gloves and catheters. Further study is needed to substantiate these findings.

Conclusion

Removal of the dry natural rubber stopper from vials did not yield solutions with less latex allergen than solutions prepared according to conventional guidelines.

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[a]Terumo Medical Corp., Elkton, MD, lot not specified.

[b]0.9% Sodium Chloride Injection Bacteriostatic, USP, 10-mL vials, SoloPak Pharmaceuticals Inc., Boca Raton, FL, lot 960517.

[c]Monoject polypropylene hub hypodermic needle, 18 gauge, 1.5 inches, Sherwood Medical, St. Louis, MO, lot not specified.

[d]0.9% Sodium Chloride Injection, USP, 250-mL Viaflex bag, Baxter Healthcare Corp., Round Lake, IL, lot C351379.

[e]Monoject tip caps, Sherwood Medical, lot not specified.

[f]Mayo Allergy Research Lab, Rochester, MN.

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