

ORIGINAL RESEARCH

Allergen vial mixing and immunotherapy: Risks of infections and vial contamination

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OBJECTIVE: To study the risks of vial contamination and infection associated with immunotherapy vial mixing and injection.

STUDY DESIGN: Retrospective review of patient immunotherapy records from January 2000-June 2006.

SETTING: Tertiary care outpatient otolaryngology clinic.

RESULTS: Two hundred seventy-two patients were given 26,795 injections (average of 98.5 injections per patient). Three hundred ninety-nine total local reactions were reported by the subjects (1.49%; 95% CI 1.34%-1.63%). The majority (82%) of the local reactions occurred during escalation dosing. There were 23 episodes of wheezing or shortness of breath after injections (9.6 of 10,000). No patients experienced anaphylaxis. There was no documented skin or systemic infections as a result of the allergy injections. None of the patients experienced fever, discharge from the injection site, cellulitis, or required antibiotics.

CONCLUSION: This review of immunotherapy records revealed no complications of infection from the preparation and administration of immunotherapy performed in an outpatient clinic.

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An estimated 7 to 10 million allergy immunotherapy injections are administered annually in the United States,¹ and typically the immunotherapy vials are prepared and administered in a physician's office. Immunotherapy has been widely practiced for decades, with the majority of practitioners performing immunotherapy vial mixing in office without the use of a hood or a clean room. However, medical practitioners are being held to increasingly stringent standards of practice by regulatory agencies, including allergy vial mixing. There have been recent attempts to put forth new guidelines that may impact allergen vial immunotherapy on both the federal and state level. The United States Pharmacopeia (USP), a nonprofit, volunteer, nongovernmental, standard-setting organization with pharmacists comprising the majority of its volunteers, issued USP <797>, a standard on medication compounding of sterile preparations in 2003.² This standard requires the use of a dedicated clean room, ventilation hood, air sampling, surface sampling, and formal testing of mixing personnel. The Joint Commission on Accreditation of Healthcare Organi-

zations (JCAHO) considers USP <797> a valuable guideline for safe practices that describe a best practice of establishing safe compounding of sterile medications.³ The Virginia Board of Medicine has moved to adopt USP <797> with a temporary exemption for allergen immunotherapy, but it is unclear if this exemption will be permanent.

Standardization guidelines to ensure patient safety that are based on scientific evidence are welcomed by both patient and physician. However, there is a lack of scientific literature that discusses the risk of local or systemic infections from allergen immunotherapy, or the need for a clean room or a hood. The purpose of our study is to determine the risks of vial contamination and infection associated with immunotherapy vial mixing and injection from current mixing practices. To the authors' knowledge, this is the first study to examine, in particular, risks of infection from current vial mixing and administration practices.

STUDY DESIGN

We performed a retrospective review of the immunotherapy injection records of all patients receiving immunotherapy injections at the Southern Illinois University otolaryngology clinic from January 2000-June 2006 after receiving approval from the local human subjects institutional review board. The immunotherapy records contained information regarding antigens contained in the vial, date of vial mixing, as well as date of injection, amount of injection, and location of injection (left or right arm). Reactions from injections were also recorded in the immunotherapy records. The injections were administered from vials mixed at the clinic in a dedicated mixing space. These vials were mixed by using sterile technique, but without the use of a sterile hood or a clean room, as described by King et al.⁴ Charts were reviewed with particular attention to possible local or systemic reactions from immunotherapy. Information was also reviewed from the patient's clinic chart and hospital records regarding possible sequelae from immunotherapy.

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RESULTS

Over a 6-year period, 272 patients were given 26,795 injections (average of 98.5 injections per patient). Of these injections, 23,981 were subcutaneous injections of immunotherapy varying in volume from 0.05 to 0.5 mL. The remaining 2814 injections were vial tests, in which a small volume from a newly mixed vial was injected intradermally to form a 4-mm wheal. Immunotherapy patients were given instructions when starting immunotherapy to report local reactions, which are defined as “an area of firmness (not necessarily redness) at the injection site larger than a 50 cent piece persisting for at least 24 hours”⁵; instructions were also given to report any respiratory or systemic reactions. Patients were observed for 20 minutes postinjection in the office. Three hundred ninety-nine total local reactions were reported by the subjects (1.49%; 95% CI 1.34%-1.63%). One hundred thirty-three of the 272 subjects (49%) had reported at least one local reaction. Sixty-one percent of the local reactions were described as being larger than a half-dollar in size; in 39 percent of local reactions patients were unable to clearly quantify size and recorded the reaction as local reaction of unknown size. The majority (82%) of the local reactions occurred during escalation, with 18 percent occurring during maintenance dosing. There were 23 episodes of wheezing or shortness of breath after injections (9.6 of 10,000). There were no reports of anaphylaxis. In 1 patient with multiple local reactions, the immunotherapy serum was sent for bacterial culture. The culture was negative and the patient continued to receive injections from that vial without further difficulty after dose adjustment. There were no documented skin or systemic infections as a result of the allergy injections.

Follow-up of these patients ranged from 5 to 60 months, during which time the patient was seen every 1 to 3 weeks. In the escalation phase, during which 82 percent of local reactions occurred, patients were seen weekly. None of the patients experienced fever, discharge from the injection area, or cellulitis. No patients required antibiotics or medical treatment for infection.

DISCUSSION

Many papers do exist that discuss the safety of immunotherapy from the standpoint of anaphylaxis and systemic reactions.⁶⁻⁹ Other papers discuss the use of glycerin as a preservative in allergen extracts and immunotherapy vials, but do not discuss the possible bacteriostatic properties of glycerin or phenol, which are included in the immunotherapy vials.¹⁰⁻¹² None of these papers discuss risk of infection, local or systemic. Our retrospective review of our immunotherapy injection records revealed no evidence of local or systemic infection transmitted by our clinic's current method of immunotherapy mixing and administration.

Our clinic mixes vials using sterile technique, but without the use of a sterile hood or a clean room, as described by

King et al.⁴ Commercially available stock vials of antigen from Antigen Laboratory (Liberty, MO) are stored in a refrigerator at 4°C. These vials contain antigen in 50 percent glycerin. The vial rubber stopper is cleaned with a 70 percent isopropyl alcohol pad, and then an aliquot of antigen is removed from this stock bottle with a 1-mL syringe and 26-gauge needle. Commercially available sterile injection vials with rubber tops are used for individual patient immunization preparations. These vials are cleaned with fresh 70 percent isopropyl alcohol pads. The previously removed antigen is then injected into the sterile patient vial. Several different antigens may be injected into these vials and diluted with sterile 0.4 percent phenolated saline buffered to pH 7.4 in a similar manner. Then 25 percent or 50 percent glycerin may be injected into the patient vial to bring the glycerin content to 10 percent. The injection is then drawn into a small-gauge (27-gauge) syringe and administered subcutaneously after the skin is prepped with 70 percent isopropyl alcohol. Doses range in volume from 0.05 to 0.5 mL. Vials are typically remixed once every 10 weeks while in the buildup phase of immunotherapy, with all vials marked with a 3-month expiration date. A small test dose, the vial test, is given from a newly mixed vial intradermally to form a 4-mm wheal prior to administration of a dose of immunotherapy from the vial. The vial is diluted 5-fold if there is a vial test in which the wheal increases in size to greater than 13 mm in 10 minutes, or discarded and remixed if there is a systemic reaction with the test dose. Patients are seen very frequently during immunotherapy, so there is repeated, short-term follow-up. Patients typically receive weekly injections during the first year of immunotherapy, every other week injections the second year, and monthly injection from years 3 to 5. Patients are monitored in the clinic for 20 minutes after injection. Patients are instructed to report local reactions, an area of induration the size of a half-dollar or greater and persisting for greater than 24 hours; they are also told to report any systemic reactions and given an EpiPen (DEY Napa, CA) with directions on use. Local and systemic reactions are typically treated by dose adjustment in the immunotherapy to a previously tolerated dose by decreasing the volume of injection from the same vial, and then increasing doses on an escalation schedule or back to a maintenance dose at subsequent visits.

Our review found local reactions greater than a half-dollar in size in 0.91 percent (245 of 26,795) and another 0.57 percent in which there were local reactions in which patients were unable to quantify the size (154 of 26,795). Wheezing or shortness of breath was reported in 0.086 percent (23 of 26,795). There were no reports of anaphylaxis in our review. Previous recent studies report local reactions in 3.16 percent and 8.3 percent; systemic reactions were present in 0.13 percent and 2.2 percent.^{13,14}

As background for this project, the authors performed a PubMed search of the English medical literature to see if data existed on infection rates for any series of intradermal

or subcutaneous injections. The assistance of a medical reference librarian was also enlisted in searching the medical and nursing literature as well. The infection control departments of 2 hospitals were contacted, and 1 hospital's regulatory affairs office to see if any internal data existed. These efforts yielded no published or internal data on infections rates following repeated subcutaneous or intradermal injections in healthy individuals.

The current series is limited in that it is a retrospective review. Reports of local reactions relied on patient self-reporting at the next visit after the reaction occurred. Self-reporting of patients may distort the true incidence of significant local reactions. Also, there were no details available on time of onset of local reactions or physical examination of local reactions, because information reviewed was from patient self-reporting of reactions that occurred in between regular immunotherapy intervals. However, the fact remains that no patient required medical treatment for infection from immunotherapy in this series. Future, prospective studies would be helpful to further study the risks of infection transmission from allergy immunotherapy and vial mixing.

The immunotherapy method used by our clinic is typical of many practitioners. The lack of reports of infectious complications from immunotherapy in the literature and in our current study suggests that infection from immunotherapy is not a clinically significant problem.

CONCLUSION

This retrospective review of immunotherapy records reveals no complications of infection from the preparation and administration of immunotherapy performed in an outpatient clinic.

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FINANCIAL DISCLOSURE

None.

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