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Review article

An evidence-based approach to medication preparation for the surgical patient at risk for latex allergy: is it time to stop being stopper poppers?

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Abstract The prevalence of latex allergy is increasing in surgical patient populations. Avoidance of exposure to the allergen is essential to minimizing perioperative complications in patients suspected to be at risk. Natural rubber latex has historically been ubiquitous in medical devices containing rubber. In 1998, the Food and Drug Administration (FDA) began to require the labeling of medical devices made from natural rubber latex; since that time substantial progress has been made in identifying latex-free alternatives. However, the rubber stoppers commonly found in pharmaceutical vial closures are exempt from FDA labeling requirements. Examination of the clinical and basic science literature regarding pharmaceutical vial closures supports limiting the rubber stopper to a single needle puncture as a safer practice, with the caveat that no strategy exists for the complete elimination of risk as long as stoppers made from natural rubber latex are used in pharmaceutical vials intended for human use.

1. Introduction

Although natural rubber latex (NRL) has been used in the manufacture of medical devices and surgical gloves for over a century, the first case of intraoperative anaphylaxis (Type I hypersensitivity) attributed to latex was not reported in the English language until 1984 [1]. Shortly thereafter, a dramatic increase in the recognition of latex-mediated anaphylaxis occurred [2]. In one decade, latex emerged as the second leading cause of intraoperative allergic reactions [3]. Constructing latex-free medical environments is the safest means of preventing allergic reactions to latex [4-6]. The reduced utilization of latex products in hospitals may have contributed to a reduction in the incidence of latex allergy among hospitalized patients [3,7], but institutions that continue to use products made from NRL continue to report allergic reactions. In a recent prospective, two-year, one-institution study of hypersensitivity reactions, latex allergy was identified in 55% of the allergic reactions occurring in patients receiving anesthesia [8]. NRL gloves are implicated in the majority of latex-mediated allergic reactions [3,9-11]. NRL gloves are also associated with causing both irritant contact dermatitis and delayed hypersensitivity (Type IV hypersensitivity), but these reactions are caused by compounds added during the manufacture of the gloves and not by the latex itself [3].

Because of the perceived risk of allergic reactions from the rubber stopper contained in some pharmaceutical vial closures, the ASA and the American Association of Nurse Anesthetists (AANA) have both issued the recommendation that rubber stoppers in pharmaceutical vials be removed prior to medication withdrawal for patients at risk for latex allergy

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[2,12]. The American Academy of Anesthesiologist Assistants does not currently offer recommendations for the preparation of medications intended for administration in latex allergic patients.[1] Similar recommendations have appeared in the British anesthesia literature [13,14]. However, the recommendation to remove the rubber stoppers is not evidence-based. Proper interpretation of the literature pertaining to administration of the medication contained in vials with stoppers made from NRL requires knowledge of the allergenicity of NRL and how it may be affected during the manufacturing process.

2. Latex allergy

NRL is derived from the milky sap of the rubber tree, *Hevea brasiliensis*. NRL is actually a mixture of naturally occurring plant-derived substances including lipids, phospholipids, carbohydrates, minerals, cis-1,4-polyisoprene and proteins in colloidal suspension. It is the residual protein that remains after processing that has been implicated in Type I hypersensitivity reactions in humans. Over 250 proteins have been identified in NRL, of which 13 have been implicated in human allergy [15]. These proteins are named "Hev b" for the species and genus of the parent plant and sequentially numbered after identification. These proteins may be found in other tropical plants and there is significant cross-reactivity between latex allergy and tropical fruit allergy (Latex-Fruit Syndrome) [3]. Latex produced from plants other than *H. brasiliensis* may differ significantly in protein content and potential for allergenicity. Synthetic latex is not derived from plant products and therefore lacks antigenic proteins.

The prevalence of seropositivity for anti-latex IgE antibodies is 6.4% among the general population [16]. Patient populations at higher risk from repeated medical or occupational exposure to latex have been well-described. The protein content of NRL has clearly been shown to be causal in the development of human latex allergy, and specific proteins have been established as the dominant allergen for various subgroups. In a particularly elegant study, demonstrated a predominance of Hev b 1 and Hev b 3 proteins (responsible for latex allergy in most spina bifida patients) on the exterior surface of 41 brands of latex medical gloves, with Hev b 5 and Hev b 6.02 (responsible for latex allergy in most afflicted health care workers) predominantly found on the interior surface of the gloves [17]. Although alternative products are currently in development, most substitutes for NRL have either failed to deliver an equivalent high elasticity-low durometer quality as NRL or have been more expensive or otherwise difficult to mass produce. NRL is still preferred for some applications for either quality or economic reasons.

[1] Allinger E. Secretary of the American Academy of Anesthesiologist Assistants, personal communication, November 16, 2008.

3. Latex manufacture

The protein content of latex made from NRL is affected by the manufacturing process. Therefore, it is necessary to know how the latex was manufactured to understand its allergenicity. Latex from *H. brasiliensis* is typically used in one of two forms. In the NRL process, latex is dipped, extruded, or coated to create highly elastic and shaped devices such as gloves, condoms, and balloon-tipped catheters. In the Dry Natural Rubber (DNR) process, latex is coagulated into dried or milled sheets and used to make syringe plungers, vial stoppers, and intravenous injection ports. The end product of the NRL process is technically a liquid; the end product of the DNR process is a solid. Whether subjected to the NRL process or the DNR process, the end product is referred to as "NRL" by the Food and Drug Administration (FDA) [18].

Vulcanization of the rubber to crosslink the polyisoprene molecules by the addition of sulfur and heat may be hastened by the addition of a variety of accelerator compounds including thiazoles, thiuram sulfides, dithiocarbamates, thiophosphates, or sulfenamides. Metal oxides may be used as activators; a variety of chemicals may be used as antioxidants, and, finally, filler compounds may be added as coloring agents including carbon black, clay, calcium carbonate, or titanium dioxide [19]. Some of these compounds are associated with delayed hypersensitivity reactions in humans. Many of these chemicals may influence the protein content of the resultant latex. For example, some additives used during the NRL process have been implicated in the rupture of lutoids within the latex, releasing the protein and causing more of the antigenic protein to be expressed on the surface of the rubber [20]. Processing temperatures and other production variables also affect protein content. Washing or chlorinating the NRL, as typically occurs during the DNR process, reduces its protein content [13,21]. Most DNR products have a protein content under 20 ug/g, whereas gloves produced by the NRL process have protein contents averaging approximately 700 ug/g [21]. The protein content of latex produced by either the NRL or DNR process may be further affected by subtle differences in its production. The extractable protein content of latex gloves varies as much as 3,000-fold between different manufacturers [9]. Although the FDA specifically prohibits the term "hypoallergenic" in describing products made from NRL [22], the allergenic potential among different forms of latex is not equivalent.

4. Labeling

In 1997, the FDA issued a rule requiring the identification and labeling of medical devices sold after September 30, 1998 that contain any rubber made by the NRL process that will have direct or indirect contact with the human body. Such items contain the notice, "Caution: This Product Contains Natural Rubber Latex Which May Cause Allergic Reactions."

Similarly, rubber created by the DNR process carries the warning: "Caution: This Product Contains Dry Natural Rubber" [22]. This rule applied only to the new sales of medical devices and did not compel the labeling of NRL and DNR in preexisting medical devices in use in hospitals. Although some older devices may contain unlabeled rubber made from NRL, this FDA regulation has simplified the identification of most rubber made from NRL.

However, several DNR items remain in clinical use at many hospitals and are not required to have the DNR cautionary label. These include the rubber stopper in some pharmaceutical vial closures and the rubber plunger in some syringes. Syringes are medical devices required to be labeled according to FDA regulations [23]. However, syringes sold prefilled with medication are regulated as "medication-device combination products" subject to different labeling requirements. Medication vial stoppers and prefilled syringes come under the jurisdiction of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), which do not currently require the labeling of DNR. The FDA rule was initially intended to apply to medication-combination devices. In response to a citizen petition and concerns from the rubber industry, the CDER elected not to require the labeling of pharmaceuticals with DNR in the rubber stoppers [24]. Similarly, the U.S. Pharmacopeia rejected a proposal to ban the use of DNR in pharmaceutical containers in 1996 [25].

5. Evidence

Two key mechanisms for contamination of liquid medication with latex protein have been proposed. The first is contamination at the time of needle puncture through the rubber stopper. The majority of the protein content of DNR lies in the interior of the rubber and might be released by violating the integrity of the surface [26]. The second mechanism is contamination with surface proteins from the stopper if the medication comes into contact with the stopper [27]. This may occur with agitation of the contents or if the vial is not constantly maintained in a vertical position during shipping or storage. Although incomplete and conflicting, there is evidence that the DNR contained in pharmaceutical vial closures may have the potential to cause adverse reactions in latex-allergic patients receiving medications packaged in those vials.

Some of this evidence has been added to the literature since the U.S. Pharmacopeia and the CDER reviewed and rejected the need for banning DNR rubber stoppers or adding cautionary warnings to the labeling of these products. However, at that time, the evidence was deemed insufficient to implicate the DNR pharmaceutical vial closures as a human health risk. A three-part analysis supported that conclusion. First, the allergenicity of rubber made from NRL positively correlated with the total content of latex protein [21].

Second, the protein content of DNR was determined to be extremely low. Significantly less protein can be extracted from DNR compared with medical gloves and other NRL products [9]. Skin testing of latex-allergic persons challenged with medications stored in vials with DNR stoppers was negative; attempts to identify latex proteins leached into medications from DNR stoppers were unsuccessful [21]. Leached latex proteins were undetectable until the DNR vial stopper had been punctured 40 times [9].

Third, the only case reports of Type I hypersensitivity from DNR in pharmaceutical vial closures in the peer-reviewed medical literature had been discredited. In one report, the rubber stopper implicated in a latex allergy actually contained no DNR, but was initially misidentified by the manufacturer and the error was not discovered until after publication [24,28-30] Table 1. In a second case report, a diabetic man with latex allergy noted improvement in a skin reaction at the site of injection after switching to an insulin preparation with a rubber stopper misidentified as non-latex [31]. The manufacturer later reported the "non-latex" rubber stopper actually contained approximately 10% DNR in combination with synthetic rubber [32].

In the decade that followed this decision, evidence has accumulated questioning each of the three pillars that support the CDER and U.S. Pharmacopeia decisions. First, total protein content of latex does correlate with allergenicity, but the amount of leachable protein is probably a more precise predictor of allergenicity [33]. The technique used to process the NRL can dramatically alter the fraction of leachable protein [34,35]. Therefore, low total protein content by itself may not be a reliable predictor of safety.

Second, Primeau et al. later showed positive skin tests in two of 12 allergic volunteers challenged with phenol-saline-human albumin that had been stored for 9 months in inverted vials with the contents in contact with rubber stoppers containing a high proportion of DNR (66% - 93%) [36]. Five of the 12 latex-allergic volunteers had positive skin reactions to solution stored in vials with rubber stoppers that were punctured 40 times with a 21-gauge needle or stored for 12 to 24 hours, inverted with the contents in contact with the stopper. Interpretation of these findings is complicated by the fact that 6 of the original 18 latex-allergic volunteers had to be excluded because of unexplained positive skin tests to saline controls, and two of the remaining 12 latex-allergic volunteers displayed positive skin tests when the solution was stored in inverted vials with non-latex bromobutyl vial stoppers. The over-sensitivity of the subjects to the non-latex challenges was poorly explained and raises questions about the validity of the positive skin tests to the latex challenge. Jones et al. identified a positive skin test in one of 39 latex-allergic individuals when challenged with solutions of bovine collagen stored in syringes with DNR plungers for three months or longer [37], providing inconclusive support of the supposition that DNR in plungers and stoppers in contact with medication may cause human allergic reaction. Terrados et al. reported a case series of 20 false-positive

Table 1 Published literature implicating DNR in pharmaceutical vial closures in human allergy

Authors	Year	Publication type	Vial	Reaction	Comments
Vassallo et al. [30]	1995	Case Report	Methylprednisolone	Anaphylaxis	Stopper misidentified as containing latex.
Towse et al. [31]	1995	Case Report	Insulin	Rash	Stopper misidentified as being non-latex.
Lear and English [42]	1995	Case Report Letter	Hep B Vaccine	Anaphylaxis	Presumed latex allergy, allergen not confirmed.
MacCracken et al. [44]	1996	Case Report	Insulin	Rash	Stopper implicated in human allergy.
Terrados et al. [38]	1997	Case Series Study	Penicillin	+ skin test	Stopper implicatecd in human allergy.
Sengewald J [45]	1997	Letter	Insulin	Unspecified	No documentation of unspecified reaction to latex in an insulin vial stopper.
Hoffman RP [46]	2000	Case Report	Insulin	Rash	Stopper implicated in human allergy.
Thomsen and Burke [41]	2000	Study	13.4 – 16% DNR stoppers	Not tested	No difference in measurable latex antigen in the medication after single puncture of the vial stopper versus removal of the stopper.
Primeau et al. [36]	2001	Study	66% – 93% DNR stoppers	+ Skin test	Skin reaction in some latex allergic volunteers after prolonged vial inversion or 40 needle punctures of the stopper.
Roest et al. [47]	2003	Case Report Letter	Insulin	Rash	Stopper implicated in human allergy.
Russell et al. [51]	2004	Case Series	Vaccines	Varied	28 possible latex allergic reactions among more than 2.5 billion vaccinations.
Trumpelmann et al. [54]	2005	Letter	Hydrocortisone	None	Possible contamination of non-latex stoppers with latex allergen during manufacture.
Wynn et al. [43]	2007	Case Report	TPN	Rash	Stopper implicated in human allergy. Clinical diagnosis not supported by laboratory testing.

penicillin skin tests in non-penicillin-allergic patients, mostly health care workers, with latex allergy. Reconstitution of the penicillin was initially performed by injecting fluid into the vial and forcefully agitating the contents against the vial stopper. Eighteen of these 20 positive skin tests reverted to negative if the penicillin reconstitution was performed outside of the vial so that agitation against the stopper was not required. The DNR content, if any, of the vial stoppers was not reported [38]. However, these reports suggest that removing the stopper may provide protection from allergic reaction in some patients.

In addition, Primeau et al. identified latex allergen at an extremely low concentration (6.7-7.4 AU/g) in phenol-saline-human albumin that had been stored in inverted medicine vials with the solution in contact with DNR for 9 months. They used a radioallergosorbent inhibition assay. Previous studies at the time of the CDER and U.S. Pharmacopeia rulings that failed to detect latex protein had relied upon the less sensitive Lowry technique [39]. However, this low concentration of latex protein is much less than the 100 AU/g that has been implicated in human allergic response after intramuscular administration [40]. Primeau et al. also did not identify latex protein in the vials with 40 needle punctures. Thomsen and Burke obtained similar results in 2000, when they investigated the need for removing the rubber vial stoppers when withdrawing medication. These investigators examined the latex protein content of 40 vials of sterile saline with DNR in the vial stoppers (13.4% - 16%), 20 accessed via a single-stick technique with an 18-gauge needle, and 20 accessed with the rubber stopper removed. These were compared with 5 controls of saline withdrawn from a needleless system (negative controls) and one sample intentionally contaminated with latex by overnight storage within a latex surgical glove (positive control) [41]. Seventeen of the 45 test vials and negative controls tested positive for latex allergen near the lower limit of sensitivity for the IgE-specific allergen inhibition immunoassay, but there was no difference between the two test groups of vials. Vials opened prior to medication withdrawal had equivalent apparent latex contamination to those in which the vial stopper containing DNR had been punctured by the needle. Additional testing suggested that all the low-level positives might have been false-positives. Latex contamination of medication could not be shown conclusively for either preparation technique.

Third, anaphylaxis has been reported from injection of the Hepatitis B vaccine in a patient later determined to be latex-allergic, but not allergic to the actual vaccine. DNR in the vaccine stopper or the syringe plunger used to administer the vaccine was suspected [42]. Latex allergy was also suspected as the etiology of a rash in a neonate receiving total parenteral nutrition (TPN) administered from a vial with a latex DNR stopper. Although the radioallergosorbent test was negative for latex antibodies, the neonate had a family history of latex allergy and the rash resolved when the TPN was administered from a vial with the stopper removed [43].

There have been case reports of skin reactions after subcutaneous insulin injection occurring in sensitive patients when the insulin was withdrawn from a vial containing a DNR stopper [44-47]. In many instances, the skin reaction does not occur when the insulin is withdrawn directly from the open vial with the stopper removed [31,45-47]. The reason allergic reaction to the latex is most often reported from insulin vials is not known. In a study of 112 pediatric patients with Type I Diabetes mellitus, latex sensitivity was most common among the subset who also had a history of atopy, but latex allergy was no more frequent than would be expected among a population of atopic or nonatopic children without diabetes [48]. DNR is preferred to synthetic rubber to prevent "coring", or stopper fragmentation, from repeated needle sticks into the multi-dose vial. Some insulin preparations are contained in vials with a high concentration of DNR for this reason and may be punctured as many as 200 times during the shelf-life of the insulin. Insulin vials with DNR stoppers may present a uniquely high risk for latex allergy in susceptible patients. The apparent clustering of case reports involving insulin vials may reflect either the large number of potential exposures to latex protein in diabetic patients from frequent self-injections or the excessive number of stopper punctures in some multidose insulin vials causing the release of latex proteins into the insulin.

Coring of the stopper could also explain the cluster of case reports involving insulin. Asakura et al. examined the incidence of microscopic stopper fragmentation with pen-type insulin injectors with an intrinsic DNR stopper in the cartridge. They demonstrated a high incidence of micro-scopic rubber fragments in the lumen of the needle prior to injection: 73% with the first puncture and 97% with the second [26]. They further reported a high, but not defined, incidence of coring when small-gauge needles used for subcutaneous injection were used to puncture DNR vial stoppers, particularly when the vials had been refrigerated. Further investigation would be needed to determine if refrigeration alters the physical properties of the rubber stopper, causing coring to occur more frequently.

The phenomenon of stopper fragmentation with injection of small fragments is hypothesized in the anesthesia literature to be a risk for sensitization of patients to latex [49,50]. The risks from exposure to DNR micro-emboli are unknown. Subcutaneous injection of DNR stopper fragments may occur commonly in diabetic patients without increasing sensitization to latex. However, even if these fragments do not predispose the patient to latex allergy, the risk from embolization of discrete rubber particles in patients with preexisting latex allergy is unknown. Micro-embolization of medication packaging is not a human health risk, but should wisely be avoided if possible.

While the evidence indicates that allergic reaction due to the latex components of a pharmaceutical vial is an infrequent event, it is difficult to determine its frequency. Analysis of the data in the Vaccine Adverse Event Reporting System (VAERS) provides further evidence that it is a very rare event [51]. Between 1991 and 2003, 160,000 adverse events related to vaccine administration were reported to the VAERS database. Of these, 28 were determined possibly to be due to latex. At least 31 vaccines available in the United States have DNR in the stopper of the vial. It was not possible from the VAERS database to determine if any of the 28 persons experiencing Type I hypersensitivity actually received a vaccine from a latex-containing vial and none of the reactions could be attributed definitely to latex. With approximately 200 million doses of vaccine administered in U.S. annually (from an unknown proportion of vials containing DNR stoppers) to a popu-lation with a latex allergy prevalence greater than 6%, 28 possible adverse events over a 14-year period represent a very low incidence of possible allergy related to pharma-ceutical vial closures [51].

6. Discussion

The DNR found in some pharmaceutical vial closures is one of the few remaining sources of unlabeled latex exposure for surgical patients in an otherwise well-labeled and sometimes latex-free hospital environment. The preponder-ance of evidence suggests that the risk of allergic reaction from the DNR in vial stoppers is small. The American Society of Hospital Pharmacists (ASHP) has advocated mandatory labeling of DNR vial stoppers [52], but regulatory organizations have not adopted this recommendation. However, the ASHP has refrained from giving their members specific guidelines for preparation of medications for latex-allergic patients, deferring to local institutional protocols, citing "the paucity of evidence that latex closures and syringe plungers are implicated in patient reactions to latex" [53]. Several strategies have been employed to minimize the risk of latex exposure to at-risk patients from the DNR in vial stoppers. These include identifying and rejecting vials with DNR vial stoppers ("catalogue-avoidance"), removing the vial stopper prior to withdrawing medication ("pop-the-top"), and limiting the vial stopper to a single needle puncture ("single stick").

"Catalogue-avoidance" is unfeasible at the point of care, since latex-containing vial closures cannot be visually identified. Although impractical for the clinician, "cata-logue-avoidance" may be successful if implemented at the institutional level [5]. Successful "catalogue-avoidance" may still miss the small risk that workers involved in its production wore NRL gloves when handling it, which has been reported in some pharmaceuticals as "latex-free" by the manufacturer [54].

While the ASA and AANA both have recommended removing the rubber stopper prior to medication withdrawal, there is insufficient evidence to conclude that this practice reduces the amount of latex allergen exposure to the patient.

Latex allergic reactions have been reported most frequently during surgery [55], but there is no evidence that the DNR contained in vial stoppers has been contributory. Latex in gloves, tourniquets, and urinary catheters are most frequently implicated in perioperative latex allergy [7]. Contamination of the medication with latex protein from the vial stopper surface has been shown when the contents are in contact with the pharmaceutical vial closure for prolonged periods of time, but the measurable level of latex protein is very low and this clinical risk would not be reduced by removing the rubber stopper immediately prior to administration. Medications should be stored in a vertical position, and a vigilant anesthesiologist may reject medications intended for use in at-risk patients that are discovered to be stored on their side or inverted immediately prior to use. However, there is currently no method to detect if a vial has been inverted or agitated at some point during shipping or storage. Moreover, the evidence is insufficient to conclude that the risk of latex protein contamination of the contents of a pharmaceutical vial with a DNR stopper is reduced by removing the stopper rather than puncturing it once with a needle.

The inadequacies of the "pop-the-top" technique extend beyond a simple lack of proven efficacy. The stoppers from pharmaceutical vials can be difficult to remove, since the manufacturer does not intend for end-user removal. The risk of microbial contamination with the "pop-the-top" rule has not been quantified. Pharmacists who employed this technique have used strict aseptic technique, specialized decapping devices, and laminar airflow hoods. Some pharmacists also have required that medication withdrawn from a vial with its stopper removed be filtered through a 0.22 μm filter to further reduce the risk of microbial contamination [56]. Even with strict aseptic technique, there is a suggestion – but not clear evidence – of an increased risk of contamination [41]. The safety of "pop-the-top" medication withdrawal at the point of care, without the precaution of laminar airflow, and using surgical instruments or other improvised devices to pry off the stopper, has not been established and should not be recommended.

Only some pharmaceutical vial closures contain latex. A measured prevalence of latex in pharmaceutical vial closures has not been reported to our knowledge, but estimations have placed it from approximately 20% [39] to greater than 50% [3]. The database, www.latexdrugs.com, contains information on the latex content of pharmaceutical vial closures for more than 90% of pharmaceuticals marketed in the U.S. Analysis of this database for pharmaceuticals available in 2007 or 2008 shows that 78% contain no DNR and 14% contain some fraction of DNR in the vial stopper. The remaining 8% could not be classified as non-latex since they contained some quantity of latex elsewhere in the packaging, had latex in only some portion of their production lots, or were to become latex-free at a future date.[2]

[2] Blevins A, www.latexdrugs.com, Personal communication, December 12, 2008.

The current evidence suggests that the "pop-the-top" approach to preparing medications for patients at risk for latex allergy is not ideal compared to the "single stick" rule combined with a prudent period of post-administration observation of the patient [39]. Even if the clinician has made every effort to avoid exposure to the patient, observation is still necessary since a small risk of latex allergy may exist if DNR is in the packaging. We emphasize that the "single stick" strategy requires a fresh stopper that has not been previously punctured. A single stick through a heavily punctured vial stopper would provide no significant advantage to the patient.

A "single stick - observation" rule has been advocated for hospital pharmacists [39]. The majority of the scientific evidence indicates that this is safe practice; this policy has been used safely for latex-allergic patients for many years. The majority of hospital pharmacies are not removing rubber vial stoppers in order to prepare medications for patients at risk for latex allergy [57], so many surgical patients will receive medications outside the operating room that are prepared under the "single stick - observation" rule. Its uniform adoption in the anesthesia community would allow for the expedient and safe administration of medications to patients at risk for latex allergy.

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