dren.[1] We concur with their conclusion that the risk of anaphylaxis from pharmaceutical vial closures is small. However, we offer our comments to their excellent discussion.

Most pharmaceutical vial closures do not contain natural rubber latex. A recent attempt to quantify the prevalence of natural rubber latex in stoppers determined that 78% of pharmaceutical products marketed in the United States contain no latex.[2] Therefore, only a minority of pharmaceutical products place patients at risk for latex allergic reactions.

The authors are correct in stating that the anaphylaxis in children that occurs immediately after intravenous administration of medication from multidose vials is rare. However, we would be reluctant to accept this as reliable evidence of safety for the subset of pharmaceutical products with natural rubber latex stoppers. Attempts to attribute causes of episodes of anaphylaxis based on the temporal relationship to an event or drug administration are perilously unreliable. In one study, anesthesiologists were only able to correctly identify the culprit allergen(s) causing intraoperative anaphylaxis for 7% of episodes; latex was among the most frequently overlooked allergens.[3] Delayed reaction to an allergen may obscure the relationship between cause and effect in the clinical setting.

There are many case reports of allergic reactions caused by latex in multidose vial stoppers used by adults, but very few reports where both the allergen and its source were definitively identified. There are fewer reports involving children. A recurring erythematous rash related to daily administration of total parenteral nutrition from a vial with a natural rubber latex stopper was reported in one infant, and this reaction was avoided by removing the stopper.[4] Although maternal latex allergy was present a radioallergosorbent test on the infant was negative, making latex allergy strongly suspected but not confirmed.

Although we wholeheartedly support the conclusion that the risk of latex allergy from medication vials is very small, we also believe it is important to emphasize that the risk is not zero. Pharmaceutical vials remain a potential source of latex exposure in many otherwise latex-free operating rooms. A high degree of suspicion for latex allergy is necessary for any episode of intraoperative anaphylaxis, and pharmaceutical vials still need to be considered as a potential source for latex allergens.

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References

1. Sampathi V, Lerman J: Perioperative latex allergy in children. Anesthesiology 2011; 114:673–80
2. Heitz JW, Bader SO: An evidence-based approach to medication preparation for the surgical patient at risk for latex allergy: Is it time to stop being stopper poppers? J Clin Anesth 2010; 22:477–83
3. Krøigaard M, Garvey LH, Menné T, Husum B: Allergic reactions in anaesthesia: Are suspected causes confirmed on subsequent testing? Br J Anaesth 2005; 95:468–71
4. Wynn RJ, Boneberg A, Lakshminrusimha S: Unexpected source of latex sensitization in a neonatal intensive care unit. J Perinatol 2007; 27:586–8

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In Reply:

I thank Drs. Heitz and Bader for their comments on the risk of allergic reactions to latex closures in multidose vials. Although latex closures have been tenuously associated with several minor allergic reactions in latex allergic patients, there has never been a report of anaphylaxis triggered by latex vial closures, which was the subject of our review. The authors are reluctant to accept our thesis that concern for latex closure-induced anaphylaxis is unwarranted, although the Food and Drug Administration found insufficient evidence that latex vial closures present a significant risk to patients with latex allergy to warrant banning their use.[1] Positive intradermal testing has been reported in patients with latex allergy who received albumin from unopened multidose vials with latex closures, but enigmatically, a positive response was also reported in several patients with latex allergy who received albumin from vials that contained nonlatex closures.[2] The latter casts doubt on the very basis for intradermal testing for latex.

To provide a rational strategy to minimize latex exposure in patients who have latex allergy, Hamilton *et al.* advocated eradicating latex from all vial closures. Until that strategy has been implemented, they recommend that we follow the "single-stick observation rule."[2] This rule assumes that all multidose vials contain latex and limits the number of punctures per vial to one. Patients who receive medication from such vials must be observed for signs of an allergic reaction for a period of time that is determined by the route of drug administration. Alternately, anesthesiologists can identify which multidose vials in their hospital contain latex closures by either requesting that their pharmacy identify those multidose vials that contain latex closures (however, a $500 fee per institution is required),* or by searching individual pharmaceutical websites† or pharmaceutical companies directly.‡ In summary, anaphylaxis remains a vanishingly small risk in patients with latex allergy who receive medications from multidose vials.

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* Available at: www.latexdrugs.com. Accessed June 15, 2011.

† Available at: www.nzgg.org.nz/guidelines/0043/appendix_1 from New Zealand. Accessed June 15, 2011.

‡ Available at: www.apppharma.com/our-products/latexinformation.html?view=list&layout=byfootnote. Accessed June 15, 2011.

References

1. Primeau MN, Adkinson NF Jr, Hamilton RG: Natural rubber pharmaceutical vial closures release latex allergens that produce skin reactions. J Allergy Clin Immunol 2001; 107:958–62
2. Hamilton RG, Brown RH, Veltri MA, Feroli ER, Primeau MN, Schauble JF, Adkinson NF Jr: Administering pharmaceuticals to latex-allergic patients from vials containing natural rubber latex closures. Am J Health-Syst Pharm 2005; 62:1822–7

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How Often Should Atenolol Be Dosed for Perioperative ß-Blockade?

To the Editor:

In "Perioperative β-blockade: Atenolol Is Associated with Reduced Mortality When Compared to Metoprolol," Wallace *et al.* make a strong case for preferring atenolol for perioperative ß-blockade.[1] As the authors note, their results are consistent with our prior meta-regression of randomized controlled trials[2] and the large observational analysis by Redelmeier.[3]

In the absence of renal insufficiency that alter the kinetics of atenolol, atenolol has favorable pharmacokinetic characteristics compared with metoprolol. However, if we are to use atenolol, we must know its optimal dosing interval. Originally, all ß-blockers were recommended for once-daily dosing[4]; however, since the early 1990s, the variable duration of ß-blockers has been recognized.[5] Some studies have found that atenolol does not provide 24 h of ß-blockade.[6,7] As Wallace *et al.* note, Freestone found that atenolol has more predictable ß-blockade at 24 h than does metoprolol.[8] However, Freestone's group also reported that atenolol's reduction of the pulse during exercise was less at 24 h than at 3 [1/2] h after dosing.[9] The INVEST study dosed atenolol twice a day if more than 50 mg per day was needed.[10]

Dr. Wallace coauthored the Multicenter Study of Perioperative Ischemia trial, which is the largest placebo-controlled trial of atenolol for perioperative ß-blockade.[11] A strength of the Multicenter Study of Perioperative Ischemia trial is continuous Holter monitoring. The Multicenter Study of Perioperative Ischemia trial dosed atenolol once per day and reported trends, although insignificant, toward increased perioperative mortality and stroke among patients treated with atenolol.[11]

Since we share Dr. Wallace's interest in atenolol, we hope he would be willing to resurrect the trial data and publish an analysis of it for diurnal variation in morbidity and electrocardiographic events in order to further evaluate the optimal dosage interval for atenolol.

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References

1. Wallace AW, Au S, Cason BA: Perioperative β-blockade: Atenolol is associated with reduced mortality when compared to metoprolol. ANESTHESIOLOGY 2011; 114:824–36
2. Badgett RG, Lawrence VA, Cohn SL: Variations in pharmacology of β-blockers may contribute to heterogeneous results in trials of perioperative β-blockade. ANESTHESIOLOGY 2010; 113:585–92
3. Redelmeier D, Scales D, Kopp A: β blockers for elective surgery in elderly patients: Population based, retrospective cohort study. BMJ 2005; 331:932
4. Kaplan NM, Lieberman E: Treatment of Hypertension: Drug Therapy, Clinical Hypertension, 5th edition. Edited by Kaplan NM. Baltimore, Williams & Wilkins, 1990: 220
5. Kaplan NM, Lieberman E: Treatment of Hypertension: Drug Therapy, Clinical Hypertension, 6th edition. Edited by Kaplan NM. Baltimore, Williams & Wilkins, 1994: 225
6. Sarafidis P, Bogojevic Z, Basta E, Kirstner E, Bakris GL: Comparative efficacy of two different β-blockers on 24-hour blood pressure control. J Clin Hypertens (Greenwich) 2008; 10:112–8
7. Neutel JM, Schnaper H, Cheung DG, Graettinger WF, Weber MA: Antihypertensive effects of β-blockers administered once daily: 24-hour measurements. Am Heart J 1990; 120: 166–71
8. Freestone S, Lennard MS, Silas JH, Ramsay LE: Duration of β-blockade with metoprolol and atenolol: Influence of drug oxidation. Postgrad Med J 1983; 59(Suppl 3):36–7
9. Silas JH, Freestone S, Lennard MS, Ramsay LE: Comparison of two slow-release formulations of metoprolol with conventional metoprolol and atenolol in hypertensive patients. Br J Clin Pharmacol 1985; 20:387–91
10. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW, INVEST Investigators: A calcium antagonist *versus* a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. JAMA 2003; 290:2805–16
11. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano DT: Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. ANESTHESIOLOGY 1998; 88:7–17

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In Reply:

The communication from Badgett *et al.* serves to emphasize that there remain a number of important questions about how to optimize the efficacy of perioperative β blockade. While it is clear that perioperative β blocker reduces mortality,[1] unresolved issues include use of prophylactic β-blockade in moderate risk patients, choice of medication, optimal dosing intervals, optimal doses, appropriate heart rate targets (*e.g.*, maximum heart rate *vs.* average heart rate), routes of administration, optimal strategies for ensuring administration, and, most importantly, strategies to avoid medication withdrawal.[1] We

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