Medical Rubber Anaphylaxis (1990, Lancet, G. Hamilton)

The following letter, published in 1990, asked Lancet readers if, when natural rubber contamination of ionic (high osmolar) radiopaque x-ray dyes is eliminated from pharmaceutical rubber, "Will North America see a significant reduction in "anaphylactic" reactions as supplies of syringes (including pre-loaded unit dose types are used up?" [An article in Radiology proved that this was true for inexpensive ionic dyes (Lasser EC, Lyon EL, Berry CC, Reports on contrast media reactions: analysis of data from reports to the U.S. Food and Drug Administration, 1990).]

The Lasser article, pointing out tghat ionic dyes were at least as safe as the expensive non-ionic dyes, has been actively suppressed into near obscurity while the marketplace has been flooded by reprints of a statistically flawed article from Japan (Katayama), which suggested that expensive non ionic dyes are much safer.

Key words
allergy, anaphylaxis (IgE-mediated), ionic and nonionic contrast agents, Japan, mercapto-benzothiazole**,** poisoning, protein-bound MBT, rubber contamination, ampoule seals, syringes, unit-dose syringes,

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Sir, – Systemic reactions from contact with rubber products have been linked to IgE-mediated allergy to raw rubber preparations.[1] In the past (e.g., for latex surgical gloves) the main allergen resulting in rubber contact dermatitis, sometimes with systemic effects, was the rubber accelerator 2-mercaptobenzothiazole (MBT).[2] [3] Twice in my diagnostic radiology practice, clusters of reactions, including anaphylaxis, have been linked to contamination of urographic contrast agents by MBT leached from rubber seals of disposable syringes and pharmaceutical vials.

2-carboxymethylthiobenzothiazole (CMB) is a direct byproduct of MBT, when pharmaceutical rubber is subjected to intense sterilization with ethylene oxide. CMB, leached primarily from disposable syringes and infusion sets, reached potentially toxic concentrations in the blood of 91 infants on a London paediatric ward.[4] Less intense ethylene oxide contamination would result in some, or much, of

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[1] Spaner D., Dolovich J., Tarlo S., Sussman G.. Hypersensitivity to natural latex. J Allergy Clin Immunol 1989; 83: 1135-1137.
[2] Fisher AA. Management of dermatitis due to surgical gloves. J Dermatol Surg Oncol 1985; 11: 628-631.
[3] Hamilton G.. Contamination of contrast agent by MBT in rubber seals. CMAJ 1987; 136: 1020-1021.
[4] Meek JH, Pettit BR. Avoidable accumulation of potentially toxic levels of benzothiazoles in babies receiving intravenous therapy. Lancet 1985; ii: 1090-1092.

the MBT being unaltered, so toxic, allergenic MBT could have reached similar concentrations.

In 1982, MBT was implicated in cell death in culture when it leached from the rubber plungers of Japanese disposable plastic syringes. The manufacturer promptly converted to MBT-free plunger material.[5] This elimination of MBT risk may explain the apparently significant drop in mortality from anaphylactoid reactions to intravenous urographic nonionic contrast agents in a large Japanese study that began on Sept. 1, 1986.[6] [7] In this same period, might Japan have experienced a related reduction in fatal reactions to other injected pharmaceuticals, once MBT had been eliminated from syringes? Will North America see a significant reduction in "anaphylactic" reactions as supplies of syringes (including, in particular, pre-loaded unit dose types) are used up?

In North America severe allergic reactions have been encountered when disposable inflatable latex retention cuffs were used for barium enemas, and before any barium had been injected. This caused one manufacturer (E-Z-M), in conjunction with US Foood and Drug Administration, to issue an urgent recall of their inflatable retention cuffs.

Raw latex often uses a sulphite as a preservative, and sulphites predispose to systemic allergic reactions, some fatal.[8] Rubber is manufactured by a crude batch processing technology that often leaves inclusions of incompletely leachable raw materials,[9] a worrying property for pharmaceutical rubber meant to come in contact with parenteral agents. The rectal mucosa is an excellent absorbing surface, and any of the allergic rubber leachables (MBT, raw latex., sulphites), appearing at random in rubber retention enema tips as a result of batch processing may cause allergic reactions when used for barium enema examinations.

Lancet readers world wide should ask governmental regulatory bodies and manufacturers when natural rubber manufactured with MBT was last used in unit-dose syringes and what are the expiry dates of the drugs involved?

References

1 Spaner D, Dolovich J, Tarlo S, Sussman G: Hypersensitivity to natural latex. J Allergy Clin Immunol 1989; 83: 1135-1137.

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[5] Graham Dt, Mark Ge, Pomeroy Ar. Chemical leaching from Terumo syringe seals. Aust NZ J Med 1982; 12: 305-306.

[6] Bettmann MA. Ionic versus nonionic contrast agents for intravenous uses: are all the answers in?. Radiology 1990; 175: 616-618.

[7] Katayama H., Yamaguchi K., Kosuka T., Takashima T., Seez P., Matsuura T.. Reactions

[8] Napke E: Stevens DGH: Excipients and additives: hidden hazards in drug products and in product substitution. CMAJ 1984; 131: 1449-1452.

[9] Blais P: The impact of medical devices on quality of pharmaceuticals. Chapter in: Quality Assurance in Pharmaceuticals Manufactured in Hospitals, eds: Warbick-Cercode A, Johnston LG (Pergamon Press, Toronto, 1985): pp 83-93

2 Fisher AA: Management of dermatitis due to surgical gloves. J Dermatol Surg Oncol 1985; 11: 628-631.
3 Hamilton G: Contamination of contrast agent by MBT in rubber seals. CMAJ 1987; 136: 1020-1021.
4 Meek JH, Pettit BR: Avoidable accumulation of potentially toxic levels of benzothiazoles in babies receiving intravenous therapy. Lancet 1985; ii: 1090-1092.
5 Graham DT, Mark GE, Pomeroy AR: Chemical leaching from Terumo syringe seals. Aust NZ J Med 1982; 12: 305-306.
6 Bettmann MA: Ionic versus nonionic contrast agents for intravenous uses: are all the answers in?. Radiology 1990; 175: 616-618.
7 Katayama H, Yamaguchi K, Kosuka T, Takashima T, Seez P, Matsuura T: Reactions to ionic and nonionic contrast media. Radiology 1990; 175: 621-628.
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9 Blais P: The impact of medical devices on quality of pharmaceuticals. Chapter in: Quality Assurance in Pharmaceuticals Manufactured in Hospitals, eds: Warbick-Cercode A, Johnston LG (Pergamon Press, Toronto, 1985): pp 83-93.