

## CORRESPONDENCE

**Warren Browner, M.D., M.P.H.**  
**Alan Go, M.D.**  
 General Internal Medicine Section

VA Medical Center, 111A1  
 San Francisco, California 94121

(Accepted for publication July 18, 1996.)

Anesthesiology  
 1996; 85:1209  
 © 1996 American Society of Anesthesiologists, Inc.  
 Lippincott-Raven Publishers

## Lack of Tolerance to Propofol

*To the Editor:*—We read with interest the report of Setlock *et al.*<sup>1</sup> concerning the lack of tolerance to repeated doses of propofol used for sedation in pediatric radiation therapy patients. We, like Setlock *et al.*,<sup>1</sup> and in contrast to Deer and Ridi,<sup>2</sup> have not seen tolerance to propofol develop in these patients. Specifically, in two recent patients accounting for more than 50 treatments, there was no increase in the induction and maintenance doses for sedation. We would like to add this experience to that of the authors.

**James F. Mayhew, M.D.**  
 Professor  
**Amr E. Abouleish, M.D.**  
 Assistant Professor  
 Department of Anesthesiology  
 The University of Texas Medical Branch at Galveston

Suite 2A John Sealy  
 301 University Boulevard  
 Galveston, Texas 77555-0591

### References

1. Setlock MA, Palmisano BW, Berens RJ, Rosner DR, Troshynski TJ, Murray K: Tolerance to propofol generally does not develop in pediatric patients undergoing radiation therapy. *ANESTHESIOLOGY* 1996; 85:207-9
2. Deer TR, Ridi GF: Propofol tolerance in a pediatric patient. *ANESTHESIOLOGY* 1992; 77:828-9

(Accepted for publication July 30, 1996.)

Anesthesiology  
 1996; 85:1209-10  
 © 1996 American Society of Anesthesiologists, Inc.  
 Lippincott-Raven Publishers

## Anaphylactoid Reactions to Protamine

*To the Editor:*—Some aspects of the interesting case report by Takenoshita *et al.*<sup>1</sup> merit, in our opinion, further discussion.

Acute reactions to protamine vary from mild reactions, such as erythema, urticaria, and transient mild elevations in pulmonary artery pressure to more severe reactions, which include bronchospasm, hypotension, and, although rare, cardiovascular collapse and death.<sup>2</sup> Protamine is also hypothesized to be a potential cause of fulminating noncardiogenic pulmonary edema after cardiopulmonary bypass.<sup>3</sup> The exact mechanisms by which protamine produces these adverse reactions are not completely understood and include direct, nonimmunologic release of histamine, immunoglobulin E (IgE)-mediated release, complement-fixing antiprotamine immunoglobulin G (IgG) antibodies, and protamine-heparin complexes that activate complement.<sup>2</sup>

The case report, as presented, contributes only partially to the understanding of adverse reactions to protamine. The acute facial edema and marked increase of tryptase in the described patient indicate a significant skin mast cell degranulation. However, an antibody-mediated mechanism is the likely cause for the increased risk of life-threatening reactions to

protamine in patients with diabetes who receive neutral protamine Hagedorn insulin.<sup>4</sup> Binding of protamine to specific IgE or possibly to subclass 4 of IgG on mast cells or basophils may result in a release of histamine and tryptase. Unfortunately, neither IgE nor IgG antibodies to protamine were determined in this case. The positive skin tests to protamine after the incident do not necessarily confirm the hypersensitivity to protamine and may only indicate previous exposure to protamine. In addition, a recent study has established a poor specificity of protamine skin tests.<sup>5</sup> Intradermal injections of protamine with concentrations between 100 and 1,000  $\mu\text{g}/\text{ml}$  induce irritative skin responses in healthy subjects<sup>6</sup>; 10  $\mu\text{g}/\text{ml}$  might have been a nonirritative concentration, although Takenoshita *et al.*<sup>1</sup> did not have control subjects to test. However, the recommended protamine test dose concentration is 1  $\mu\text{g}/\text{ml}$ .<sup>5</sup> In addition, out of the 11 patients taking neutral protamine Hagedorn insulin who had severe anaphylactoid reactions to protamine, only one of four patients studied by cutaneous testing had clearly positive results.<sup>2</sup>

In summary, the case report identifies a patient with neutral protamine Hagedorn insulin-dependent diabetes mellitus who suffered a