

Anesthesiology  
63:351-352, 1985

## *Anaphylactoid Reactions and Histamine Release by Barbiturate Induction Agents: Clinical Relevance and Patho-mechanisms*

THERE IS AN INCREASING awareness of adverse reactions and the importance of histamine release in anesthesia and surgery. Over the past 15 years, numerous case reports, epidemiologic studies, and surveys, including a number of randomized controlled clinical trials, have appeared in the literature.<sup>1</sup> Recent removal of Althesin® and propanidid from clinical practice in Europe, as well as the increased appreciation of the frequency of these adverse reactions, prompted a recent conference in Nancy, France, attempting to establish the clinical relevance and pathophysiology of histamine release in the perioperative period.<sup>2</sup> Investigators from the United States, Western Europe, and Australia shared their data on this subject. Understandably, anesthetists are reluctant to report adverse reactions.

Some of this reluctance may arise from an inability to interpret the clinical signs of anaphylactic or anaphylactoid reactions. Case reports on thiopental reactions are quite numerous, as Hirshman *et al.*<sup>3</sup> indicate in this issue and others have previously documented. Nevertheless, the drug has been used and in widespread practice for many years and has been recommended as an essential drug by the World Health Organization in 1979. Methohexitone is considered to be even safer, yet there are reports in the literature suggesting that this drug may be more likely to cause allergic or pseudoallergic reactions.<sup>4</sup> Thiamylal and pentobarbitone are less frequently involved in these reactions.<sup>5</sup> Hence, the information available in the clinical literature on adverse reactions to barbiturates may not represent an accurate picture of the incidence of such

reactions but may be biased by the patterns of usage that occur throughout different countries.

While many clinical mediators have been implicated in allergic or pseudoallergic reactions, most of the animal studies have not been verified in humans.<sup>6</sup> The established criteria for ascertaining and describing a mediator are derived from Koch and Dale (presence in disease, absence in health, eliciting disease by exogenous administration, and blocking the effect by antagonists and preventing disease). These criteria have been fulfilled in humans only for histamine and only for a small number of anesthetic drugs (propanidid, polygeline,<sup>6</sup> and morphine<sup>7</sup>). The ability to assay plasma histamine has been essential in fulfilling these rigorous criteria.<sup>1</sup> Similar studies have been performed with thiopentone and methohexitone.<sup>8</sup> Elevated plasma histamine levels were demonstrated in nine of 10 human volunteers following the administration of thiopentone and in six of eight patients following methohexitone administration. In addition, gastric acid secretion has been used as a clinical marker for histamine release following the administration of thiopentone.<sup>9</sup> Thus, there is substantiating data in the clinical literature for barbiturate-induced histamine release, which has been demonstrated in this study by Hirshman *et al.*<sup>3</sup> *in vitro*.

Several mechanisms have been proposed for histamine release by barbiturates in clinical conditions.<sup>1,2,4,10</sup> Pseudoallergic (nonimmunologic) interactions with human mast cells *in vivo*<sup>9,10</sup> have been substantiated by the study of Hirshman *et al.*<sup>3</sup> for thiopentone in isolated cells. However, methohexitone was ineffective *in vitro*. The marked heterogeneity of mast cells and basophilic granulocytes<sup>1</sup> with regard to their response to histamine release could explain these differences. It is possible that the foreskin model will not serve to identify the full extent to which anesthetic agents may induce histamine release.

In addition to the possible pseudoallergic mechanisms, Watkins<sup>10</sup> indicates that approximately 50% of thiopentone

Accepted for publication June 12, 1985.

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Key words: Anesthetics, intravenous: methohexital; pentobarbital; thiamylal; thiopental. Histamine: mast cells; release.

tone reactions are mediated by IgE antibodies or immunocomplexes and that there is activation of the complement system by the classical and alternate pathway. The same ratio between allergic and pseudoallergic reactions has been demonstrated for methohexitone by the same author. Fatal reactions to thiopentone were shown to be more likely to be due to allergic than to nonimmunologic mechanisms. Hence, the greater safety of methohexitone over that of thiopentone in clinical conditions cannot be deduced from the *in vitro* studies but only from randomized clinical trials.

Clinicians confronted with a plethora of case reports on adverse reactions and numerous *in vitro* reports such as that of Hirshman *et al.*<sup>5</sup> may be somewhat bewildered as to how to alter their clinical practice. Is this histamine release important? The clinical literature reveals 23 prospective and randomized clinical trials on volunteers and patients in which the incidence of histamine release was 20–30%.<sup>8</sup> The extent of clinical symptoms depended on the amount of histamine that was released. The systemic responses ranged from 1 to 5%, with life-threatening responses from 0.1 to 0.5%. Clinicians have the responsibility to select which, from a variety of drugs, will be the safest overall. For those patients who may be compromised cardiovascularly, it is clear that selecting a drug with less histamine release may be an appropriate choice. Another strategy for maintaining hemodynamic stability involves the prophylactic use of histamine H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists, always in combination, which have been shown to be safe and effective<sup>1,2,7,8</sup> and may be used for patients at risk when it is absolutely necessary to give drugs with histamine-releasing potency.

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