more important. This is necessary since on the one hand it will be easy to overdose with the new agents because their side effects are minimal. On the other hand, many operations may be performed without the need for reversal of residual block (because recovery is relatively rapid) if supplemental doses of the new drugs are precisely timed as indicated by monitoring techniques. Train-of-four monitoring and counting of the number of responses visible in the train will be just as applicable in the case of the new nondepolarizing as in the use of current drugs. Fourth, intubation of the trachea with nondepolarizing relaxants will become more common, since the new intermediate-duration agents make it possible to achieve the depth of paralysis required for this maneuver without the consequence of very long-duration neuromuscular blockade. For those anesthetists still preferring succinylcholine for intubation because of its fast onset and the convenience of fasciculations heralding the onset of block, the new intermediate-duration nondepolarizers will still provide convenient maintenance of relaxation after intubation because of their lack of cumulative tendency. In fact, this property has already suggested that maintenance of relaxation by continuous infusion of noncumulative nondepolarizing relaxants may become commonplace.

The new relaxants are part of a wave of pharmacologic innovation currently sweeping our specialty. Together with new narcotic analgesics, new induction agents, and new inhalation anesthetics, the new neuromuscular blocking drugs promise to revolutionize the practice of anesthesia.

JOHN J. SAVARESE, M.D.
Associate Professor of Anesthesia,
Harvard Medical School;
Associate Anesthetist at the Massachusetts General Hospital
Boston, Massachusetts

References

Anesthesiology
55:3-5, 1981

Anaphylactoid Reactions to Anesthetic Drugs

Histamine is distributed throughout the human body and is present in potentially lethal quantities in organs that are particularly vulnerable to its actions, e.g., the airways, blood vessels, and heart. Most of it is sequestered with heparin in small membrane-bound granules in mast cells (3–20 pg histamine/cell). These cells are embedded in the mucosal linings, skin, connective tissue, adventitia of small blood vessels, and

Accepted for publication December 22, 1980.

0003-3022/81/0700/0003 $00.65 © The American Society of Anesthesiologists, Inc.
conducing bundles of the heart. The widespread distribution of histamine in the mast cell is observed only in terrestrial vertebrates, but whatever the benefit of this particular development in vertebrate evolution, the mast cell is of practical importance to the clinician because of its ability to degranulate in response to allergic reactions and a wide variety of drugs. In one recent report, 10 per cent of all hospital admissions were due to adverse reactions to therapeutic doses of drugs, and of these, 48 per cent were attributed to an anaphylactic-type reaction.

In the true allergic reaction, certain classes of antigens and drugs, which form hapten-protein conjugates (e.g., penicillin, cephalosporin, and the anticancer alkylating agents), stimulate production of complementing IgE antibodies which become fixed to membrane receptors on the mast cells. Re-exposure to antigen leads to aggregation of the bound IgE molecules and a rapid extrusion of mast cell granules into tissue spaces by a Ca²⁺, energy-dependent process. If release is localized, redness, uticaria, itching, sneezing, and constriction of the airways will result but, if release is generalized, the effects are more severe and include extensive flushing, headache, tachycardia, hypotension, loss of serum through the opening of numerous pores in the capillary bed, and, in some patients, cardiac arrest and irreversible shock. These effects are due largely to release of histamine and its interaction with two types of histamine receptors, H₁ and H₂. Administration of an antagonist of both H₁ (e.g., mepyramine and benadryl) and H₂ (e.g., cimetidine and drugs undergoing clinical trials—oxetidine, pimecetidine and ranitidine) receptors will ameliorate many but not all symptoms of the allergic reaction. Biologically active lipids such as prostaglandins, leukotrienes (SRS-A), and platelet-activating factor (PAF), as well as chemotactic factors and hydrolytic enzymes are released along with histamine. If administered early, epinephrine is the most useful antidote, as it will abort the entire degranulation process through the β-adrenergic receptor-mediated stimulation of cyclic AMP production.

Of more concern to anesthesiologists, however, is another type of reaction in which drugs act directly on the mast cell to produce an “anaphylactoid” reaction. The mechanism of release is not understood but mimics induced by IgE and antigen in that release requires Ca²⁺ ions, is energy-dependent, and can be suppressed by agents that increase mast cell cyclic AMP levels. These drugs (see below) have been widely studied in animal models, but there are too little data to know to what extent these drugs are a problem in humans. It is hoped that the article by Moss et al. in this issue and the comments here will stimulate further interest in this subject.

The histamine-releasing drugs include many familiar to anesthesiologists such as morphine, codeine, and meperidine; the quaternary ammonium compounds, d-tubocurarine, succinylcholine, hexamethonium, and gallamine; sympathomimetic drugs; dichloroisoproterenol; the phenothiazines; antihypertensive drugs; the alkaloids, atropine, papaverine, quinine, and reserpine; basic antibiotics; surface active agents, Tween 20, and bile salts; and the plasma expanders, dextran and polyvinyl pyrrolidone. To this list we can now add radiopaque substances, adriamycin and similar antibiotics, certain solubilizing agents, and a number of short-acting intravenous anesthetics, some of which have been used in humans. The structures of these drugs are so diverse that Paton was forced to conclude that in addition to polymeric substances, “any compound with two or more basic groups, separated by a sufficient aromatic or aliphatic scaffold is liable to have this property;” even today our knowledge of the structure-activity relationships is still elementary.

The main reason, apart from ethical concerns, for the limited studies in human subjects has been the lack of a sufficiently sensitive and specific assay for histamine in body fluids. The recent refinements of the radioenzymatic assay no longer make this a problem. The assay does not require experience beyond that found in the normal hospital or commercial laboratory and is sufficiently sensitive to assay plasma histamine levels down to 1 or 2 ng/ml. Several recent studies with the enzymatic assay show an excellent correlation between changes in histamine levels in plasma and tissue fluids and clinical symptoms in patients with physical urticarias and anaphylactic reaction to succinylcholine. For those who wish to establish basal histamine levels with a high degree of precision, the additional steps described by Moss and co-workers in this issue seem to be advantageous. As collection of blood specimens pose no difficulty in the operating room, detection of histamine release during an adverse drug reaction could become a routine procedure.

If it is thought that anaphylactoid reactions are little more than a manageable nuisance, two studies can be cited to indicate otherwise. Levi and his group have shown that, at least in animals, the release of a portion of the endogenous histamine in the heart will lead to severe cardiac dysfunction, with arrhythmias, prolongation of A-V conduction, and cardiac arrest. Lorenz and his associates report that, of four patients who exhibited anaphylactoid reactions to an intravenous anesthetic, two underwent cardiac arrest. Only small perturbations in plasma histamine levels are needed to produce these reactions. Increases in plasma histamine levels from 0.3 to 2–3 ng/ml are sufficient to induce gastric secretion and gastric discomfort. Increases of 2–5 ng/ml are invariably associated
with tachycardia, widespread flushing and urticaria, and increases above 5 ng/ml with severe hypotension. Normal histamine levels appear to be in the range of 0.3–1.0 ng/ml.

The paper by Moss and associates is a well-designed study from which one can predict the extent of the problem with one drug, d-tubocurarine. Their data indicate that in humans, as in experimental animals, the response to this drug is dose-related and that, with sufficiently high therapeutic doses (0.6 mg/kg), a measurable response is provoked in all patients. It is hoped that similar data will be forthcoming for other suspect drugs. Additional observations on the relationship of rates of drug administration to histamine release would also be helpful. Experience has taught us that reactions are more readily provoked by bolus injections (where transient high levels of drug might trigger mast cell degranulation) than with slow infusions, where plasma drug levels are held at less critical levels.

In view of the limited clinical data, what recommendations can be made? As anaphylactoid reactions are seen in healthy as well as sick individuals, slower rates of infusions of suspect drugs in all patients might be advisable. Premedication with both H1 and H2 histamine antagonists should certainly be considered in patients with cardiovascular problems. Other factors to consider are that high circulating levels of glucose and epinephrine block release, whereas the tendency of mast cells to degranulate is much enhanced by low humidity (as in exercise-induced asthma), low circulating levels of epinephrine, hypoglycemia, cholinergic agents, and ethanol. In this context, the effects of gaseous anesthetics need to be studied.

MICHAEL A. BEAVEN, PH.D.
Laboratory of Cellular Metabolism
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

References