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[16] and counting of the number of responses visible in the train[17] will be just as applicable in the case of the new nondepolarizers 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[4] 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

1. Savarese JJ, Kitz RJ: Does clinical anesthesia need new neuromuscular blocking agents? ANESTHESIOLOGY 42:236–239, 1975
2. Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (Norcuron™): A new nondepolarizing relaxant. ANESTHESIOLOGY 55:6–11, 1981
3. Lee-Son S, Waud BE, Waud DR: A comparison of the neuromuscular blocking and vagolytic effects of ORG NC45 and pancuronium. ANESTHESIOLOGY 55:12–18, 1981
4. Agoston S, Salt P, Newton D, et al: The neuromuscular blocking action of ORG NC45, a new pancuronium derivative, in anaesthetized patients. Br J Anaesth 52:535–595, 1980
5. Durant NN, Marshall IG, Savage DS, et al: The neuromuscular and autonomic blocking activities of pancuronium, ORG NC45 and other pancuronium analogues in the cat. J Pharm Pharmacol 31:831–837, 1979
6. Savage DS, Sleigh T, Carlyle I: The emergence of ORG NC45, 1-{(2β, 3α, 5α, 16β, 17β)-3,17-bis (acetyloxy)-2-1-piperidinyl)-androstan-16-yl}-1 methylpiperidinium bromide, from the pancuronium series. Br J Anaesth 52:35–95, 1980
7. Hughes R, Chapple DJ: The pharmacology of atracurium, a new competitive neuromuscular blocking agent. Br J Anaesth 53:31–44, 1981
8. Payne J, Hughes R: The evaluation of atracurium in anesthetized man. Br J Anaesth 53:45–54, 1981
9. Hughes R, Payne JP: Clinical studies with atracurium, a new competitive neuromuscular blocking agent. ANESTHESIOLOGY 53:S272, 1980
10. Hunt TM, Hughes R, Payne JP: Preliminary studies with atracurium in anaesthetized man. Br J Anaesth 52:238P, 1980.
11. Savarese JJ, Wastila WB: BWA444U: An intermediate-duration nondepolarizing neuromuscular blocking agent with significant lack of cardiovascular and autonomic effect. ANESTHESIOLOGY 51:S279, 1971
12. Alant O, Darvas K, Pulay I, et al: First clinical experience with a new neuromuscular blocker pipecurium bromide. Arzneim Forsch 30:374–379, 1980
13. Karpati E, Biro K: Pharmacological study of a new competitive neuromuscular blocking steroid, pipecurium bromide. Arzneim Forsch 30:346–354, 1980
14. Savarese JJ, Wastila WB: Pharmacology of BW785U: a short-acting nondepolarizing neuromuscular blocking agent. ANESTHESIOLOGY 51:S277, 1979
15. Savarese JJ, Ali HH, Basta SJ, et al: Clinical neuromuscular pharmacology of BW785U, an ultra-short-acting nondepolarizing ester neuromuscular blocking agent. ANESTHESIOLOGY 53:S274, 1980
16. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block (Part I). Br J Anaesth 43: 473–477, 1971
17. Lee C: Train-of-four quantitiation of competitive neuromuscular block. Anesth Analg (Cleve) 54:649–653, 1975

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.

conducting bundles of the heart. The widespread distribution of histamine in the mast cell is observed only in terrestrial vertebrates,[1,2] 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, 4 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.[3]

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 complementary 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 Ca^{++}, energy-dependent process.[4] 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.[4] These effects are due largely to release of histamine and its interaction with two types of histamine receptors, H_1 and H_2.[5] Administration of an antagonist of both H_1 (*e.g.*, mepyramine and benadryl) and H_2 (*e.g.*, cimetidine and drugs undergoing clinical trials—oxmetidine, picometidine 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.[4,6-8] 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.[4]

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.[9] The mechanism of release is not understood but mimics that induced by IgE and antigen in that release requires Ca^{++} 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,[10,11] 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.*[12] 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.[10,11] 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 studied in humans.[9] The structures of these drugs are so diverse that Paton[10] 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.[13] 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[6,14,15] and anaphylactic reaction to succinylcholine.[16] For those who wish to establish basal histamine levels with a high degree of precision, the additional steps described by Moss and co-workers[12] 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.[17] Lorenz and his associates report that, of four patients who exhibited anaphylactoid reactions to an intravenous anesthetic, two underwent cardiac arrest.[9] 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.[9] Increases of 2–5 ng/ml are invariably associated

with tachycardia, widespread flushing and urticaria, and increases above 5 ng/ml with severe hypotension.[4,9,13] Normal histamine levels appear to be in the range of 0.3–1.0 ng/ml.[9,12,13]

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 transiently 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 H_1 and H_2 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

1. Reite OB: Comparative physiology of histamine. Physiol Rev 52:778–819, 1972
2. Almeida AP, Beaven MA: Phylogeny of histamine in vertebrate brain. Brain Res 208:1244–1250, 1981
3. Levy M, Lipshitz M, Eliakim M: Hospital admissions due to adverse drug reactions. Am J Med Sci 177:49–56, 1979
4. Beaven MA: Histamine: Its role in physiological and pathological processes. Monogr Allergy 13:1–114, 1978
5. Black JW, Duncan WAM, Durant GJ, et al: Definition and antagonism of histamine H_2 receptors. Nature 236:385–390, 1972
6. Soter NA, Wasserman SI, Austen KF, et al: Release of mast-cell mediators and alterations in lung function in patients with cholinergic urticaria. N Engl J Med 302:604–608, 1980
7. Austen KF: Biologic implications of the structural and functional characteristics of the chemical mediators of immediate-type hypersensitivity. Harvey Lect 73:93–161, 1979
8. Demopoulis CA, Pinkard RN, Hanahan DJ: Platelet-activating factor. Evidence for 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine as the active component (a new class of lipid chemical mediators). J Biol Chem 254:9355–9388, 1979
9. Lorenz W, Doenicke A, Schoning B, et al: The role of histamine in adverse reactions to intravenous agents, Adverse Reactions of Anaesthetic Drugs. Edited by Thornton A. Amsterdam, Elsevier/North-Holland Biomedical Press, 1980, pp 169–237
10. Paton WDM: The mechanism of histamine release, Ciba Foundation Symposium on Histamine. Edited by Wolstenholme GEW, O'Connor CM. Boston, Little Brown, 1956, pp 59–73
11. Rothschild AM: Histamine release by basic compounds, Handbook of Experimental Pharmacology, Histamine and Antihistamines, Vol. XVIII/part 1. Edited by Rocha e Silva M. Berlin, Springer-Verlag, 1966, pp 386–430
12. Moss J, Rosow CE, Savarese JJ, et al: Role of histamine in the hypotensive action of *d*-tubocurarine in humans. ANESTHESIOLOGY 55:19–25, 1981
13. Shaff RE, Beaven MA: Increased sensitivity of the enzymatic isotopic assay of histamine: Measurement of histamine in plasma and serum. Anal Biochem 94:425–430, 1979
14. Kaplan AP, Beaven MA: *In vivo* studies of the pathogenesis of cold urticaria, cholinergic urticaria and vibration induced swelling. J Invest Dermatol 67:327–332, 1976
15. Kaplan AP, Horakova Z, Katz SI: Assessment of tissue fluid histamine levels in patients with urticaria. J Allergy Clin Immunol 61:350–354, 1978
16. Moss J, Fahmy N, Sunder N, et al: Hormonal and hemodynamic profile of an anaphylactic reaction in man. Circ Res, 63:210–213, 1981
17. Zavecz JH, Levi R: Separation of primary and secondary cardiovascular events in systemic anaphylaxis. Circ Res 40: 15–19, 1977