

HISTAMINE RELEASING POTENCIES OF ATRACURIUM AND VECURONIUM

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Few drugs introduced in anaesthesiology have changed its practice as significantly as the muscle relaxants. Until curare was first used by Griffith in 1942, muscle relaxation during surgical procedures was produced mainly by deep anaesthesia. It was frequently associated with undesirable side-effects. Although muscle relaxants are universally used today, still have many draw-backs. Succinylcholine has been found to be with side-effects such as increased intraocular pressure, hyperkalemia which may result in cardiac arrest, bradycardia, increased intragastric pressure, myoglobinuria and prolonged muscle weakness and muscular pain. d-Tubocurarine has been reported to cause symptoms of histamine release, hypotension and prolonged depression of neuromuscular function. For this reason pharmacologists and anaesthesiologists have directed their efforts towards the development of neuromuscular blocking drugs free of such side-effects. Another major reason for developing new neuromuscular blocking agents is that all currently used drugs have well known cardiovascular effects, some of which may be related to the release of histamine. This review is undertaken to discuss the abilities of two neuromuscular agents, Atracurium (AT) and Vecuronium (VC) to release histamine with the help of the results of the studies which were reported in recent years.

Histamine is largely contained in the fixed mast cells and the circulating basophils of the blood. By its action on smooth muscles it causes vasodilatation and permits the movement of phagocytic cells across the tissues to their site of action during the inflammatory response. In man, the basal histamine level is around 0.4 mg ml^{-1} plasma. Additional release of only 1 to 2 ng ml^{-1} of histamine causes marked clinical manifestations (1, 2). At concentrations greater than 30 ng ml^{-1} plasma in addition to the basal level, life-threatening situations are almost certainly present (2). Release of endogenous histamine may cause the following effects in man: a) Vasodilatation (H_1 and H_2 receptors), b) Positive inotropy (H_2 receptors of atria and ventricles), c) Positive chronotropy (H_2 receptors of atria), d) Adenylate cyclase stimulation (H_2 receptors of ventricles), e) Coronary vasodil

ation (H_2 receptors), f) Coronary vasoconstriction (epicardial H_2 receptors), g) Alteration of dysrhythmic potentials (H_1 and H_2 receptors), h) Increased serum catecholamines (H_1 receptors of adrenal medulla), i) Bronchoconstriction in susceptible individuals (H_1 receptors) and j) Skin erythema (H_1 and H_2 receptors) (3, 4).

Cardiac dysrhythmia is one of the most serious reactions which can be seen due to histamine liberation. Arrhythmogenic effects of histamine include enhancement of normal automaticity, induction of triggered tachyarrhythmias, depression of atrioventricular conduction and increase in the vulnerability of the ventricles to fibrillation (5).

There is an accepted belief that histamine release is harmful and that drugs which, in skin tests, produce histaminoid weals are nonpreferable. Such release may be achieved with intravenous substances in as many as 1 out of 3 patients, but these reactions seem to be self-limiting (1, 6, 7).

Almost all known muscle relaxants lead histamine liberation at various degrees. So they may cause clinical manifestations varying from skin flushing to cardiac arrest. For example, the main unwanted effects of tubocurarine are release of histamine and ganglionic blockade. Both of these two effects may cause severe hypotension (8, 9). Metocurine is the O,O,N-trimethyl analogue of tubocurarine and can also release histamine, but generally there is a wider margin between the undesirable effects and the neuromuscular blocking dose (9). Although there are a few reports about bronchospasm after pancuronium injection, there is an accepted belief that histamine release does not cause difficulty with either gallamine or pancuronium (9, 11).

ATRACURIUM AND VECURONIUM

AT and VC are neuromuscular blocking drugs with intermediate duration of action and have been introduced recently to the clinical practice (9, 12, 13, 14). Their histamine liberating effects have been well defined by many authors. Although some workers have equated AT and VC in their ability to liberate hista-

mine, others have found AT to be more potent in this regard.

In a trial done by Goudsouzian and his co-workers (16) in 1986 the histamine releasing potential of equivalent bolus doses of AT (0.6 mg kg^{-1}) and VC (0.12 mg kg^{-1}) had been evaluated in 20 children anaesthetized with Halothane. None of the 10 patients receiving VC had significant increase in plasma histamine concentration. In 2 of the 10 children receiving AT, plasma histamine concentration increased markedly without any apparent clinical manifestations. On the other hand, it seems likely that, children differ from adults in regard to the side-effects associated with the release of histamine. For example, hypotension and the skin rashes seem to be rare in children whereas occasional in adults (16, 17). Most of the histaminomimetic reactions in children have been observed locally along the injected vein (18, 19). It is unclear, whether this difference is attributable to release of less histamine in children or whether the child's end organs are simply less responsive (15).

Lavery et al. (20), investigated histaminoid responses after intradermal and subsequent intravenous administration of AT and VC in 80 patients. Intradermal AT and VC produced positive responses in 40 and 7 patients respectively. Generalized erythema occurred in 27 patients after intravenous AT and only in 1 patient after intravenous VC. These results confirm that AT frequently triggers cutaneous histamine liberation. But they couldn't observe any symptoms of changes in bronchometer or cardiovascular disturbances.

In a case report presented by Lavery, Boyle and Mirakhur (21) in 1985, the workers have described skin rashes, hypotension and bronchospasm after the administration of AT and thiopental.

Basta and Savarese (3) tried to compare the potency of histamine releasing ability of several muscle relaxants and to correlate cardiovascular effects with serum histamine levels. They found that, AT (0.6 mg kg^{-1}) caused statistically significant changes in heart rate, mean arterial pressure and plasma histamine levels. VC at $0.1 - 0.2 \text{ mg kg}^{-1}$ doses did not alter plasma histamine concentrations.

In another study (4), relative abilities of AT and dimethyltubocurarine to release histamine; and resultant cardiovascular effects correlated with serum histamine concentrations were evaluated. Consequently they observed that, the dose of the neuromuscular blocking agent which increases plasma histamine to about 200% of control values resulted in clinically and statistically significant changes in heart rate and arterial pressure; and maximum heart rate and arterial pressure changes occurred 1 - 2 minutes after AT and tubocurarine injection and returned to normal within 5 minutes. The ability of AT to release histamine was approximately equal to one third of that of tubocurarine.

In clinical practice, intradermal injections of diluted drug solutions are used to investigate the histamine releasing abilities of drugs. In prospective trials, a high incidence of wheal and flare reactions were observed towards AT but not VC as expected. On this basis, it can be proposed that VC was likely to be the safer drug to be used clinically. On the other hand we believe that, skin tests are not of value to make final decision for any drug tested in this regard, since drugs pethidine and atropine with low incidence of anaphylactoid reactions when administered intravenously, produce wheal and flare reactions when injected intradermally.

Under the light of all these studies it can be seen that, the histamine releasing ability of AT is more than VC. But AT doses have a tendency to produce a high incidence of cutaneous manifestations, the majority of which are harmless allergic reactions resulting in local skin histamine rather than plasma histamine release. On the other hand if plasma histamine levels are measured correctly following AT administration they are not found to be greater than those encountered with althesin, thiopental, pancuronium or even fentanyl (1).

Consequently it can be said that, VC does not alter serum histamine levels even at the upper extreme of the clinical dose range. The results confirm that, AT frequently triggers especially cutaneous histamine liberation at 0.6 mg kg^{-1} doses and this was rarely associated with the changes in bronchometer or serious cardiovascular disturbances. But we have to say that, for short procedures where suxamethonium has to be avoided, VC might be a better choice than AT.

On the other hand, if it is necessary to use AT as a muscle relaxant, many of the relatively minor histaminoid adverse effects of AT can be avoided by:

- Care in preventing drug mixing (especially with thiopental) in the cannulae by flushing saline (1, 2).
- Slow administration of the drugs (1, 15, 21).
- Use combinations with other drugs with low histamine releasing potential (e.g. etomidate) to reduce additive side-effects (1).
- Histamine release can be blunted by giving both H_1 and H_2 receptor antagonists prior to administration of AT (21).
- Large bolus doses of AT should best be avoided in asthmatic patients, since such a dose may possibly trigger an attack (15).

REFERENCES

- Watkins J. *Histamine release and Atracurium. Second International Atracurium Symposium. Abstract Proceedings, Review By Wellcome Company. Montreux, 2 - 5 October 1985.*
- Watkins J. *Histamine release and Atracurium. Br J Anaesth. 1986; 58 : 19S - 22S.*
- Basta SJ, Savarese JJ. *Comparative histamine releasing properties of Vecuronium, Atracurium, Tubocurarine and Metocurine. Clinical Experiences With Norcuron Symposium. Abstract Pro-*

- ceedings, Review By Organon Teknika and Organon Inc. Geneva, 21 - 22 April 1983.
4. Basta SJ, Savarese JJ, Ali HH, Moss J, Gionfriddo M. Histamine releasing potencies of Atracurium, dimethyltubocurarine and tubocurarine *Br J Anaesth.* 1983; 55 : 105S.
 5. Levi R, Aida A, Trzeciakowski JP, Guo ZG, Aaronson LM, Luskind RD, Lee CH. Disrhythmias caused by histamine release in guinea pig and human hearts. *Klin Wochenschr.* 1982; 60 : 965 - 71.
 6. Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anaesthesia. *Anaesthesiology.* 1982; 56 : 93 - 96.
 7. Moss J, Rosow CE, Savarese JJ, Philbin DM, Kniffen DJ. Role of histamine in the hypotensive action of d-tubocurarine in man. *Anesthesiology.* 1981; 55 : 19 - 25.
 8. Farmer BC, Sivarajan MS. An anaphylactoid response to a small dose of d-tubocurarine. *Anesthesiology.* 1979; 51 : 358 - 59.
 9. Durant NN, Katz RL. Non-neuromuscular effects of Vecuronium and other competitive muscle relaxants. *Clinical Experiences With Norcuron Symposium. Abstract Proceedings, Review By Organon Teknika and Organon Inc. Geneva, 21 - 22 April 1983.*
 10. Heath ML. Bronchospasm in an asthmatic patient following pancuronium. *Anaesthesia,* 1973; 28 : 437 - 40.
 11. Churchill-Davidson HC. Neuromuscular blocking drugs. *A Practice of Anaesthesia. Fourth Edition. London: Lloyd-Luke Ltd., 1984: 861 - 911.*
 12. Cronnelly R, Fisher DM, Miller RD, Gencarelli P, Nguyen Gruerke L, Castagnoli N. Pharmacokinetics and pharmacodynamics of Vecuronium and pancuronium in anaesthetized humans. *Anesthesiology.* 1983; 58 : 405 - 408.
 13. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE. Clinical pharmacology of Atracurium besylate (BW 33A) : A new non-depolarising muscle relaxant. *Anaesth Analg.* 1982; 61 : 723.
 14. Payne JP, Hughes R. Evaluation of Atracurium in anaesthetized man. *Br J Anaesth.* 1981; 53 : 45.
 15. Goudsouzian NG, Young ET, Moss J, Liu LPM. Histamine release during the administration of Atracurium and Vecuronium in children. *Br J Anaesth.* 1986; 58 : 1229 - 33.
 16. Goudsouzian NG, Liu NPM, Gionfriddo M, Rudd GD. Safety and efficacy of Atracurium in adolescents and children anaesthetized with Halothane. *Anesthesiology.* 1983; 53 : 459.
 17. Savarese JJ. Metocurine in infants and children. *Neuromuscular and clinical effects. Anaesthesiology.* 1978; 49 : 266.
 18. Nightingale DA, Bush GH. A clinical comparison between tubocurarine and pancuronium. *Br J Anaesth.* 1973; 45: 63.
 19. Goudsouzian NG, Young ET, Moss J, Liu LPM. Atracurium in paediatric anaesthesia. *Br J Anaesthesia.* 1983; 55 : 115S.
 20. Lavery GG, Clarke RSJ, Watkins J. Plasma IgE levels and histaminoid responses to Atracurium and Vecuronium. *Second International Atracurium Symposium. Abstract Proceedings, Review By Wellcome Company. Montreux, 2 - 5 October 1985.*
 21. Lavery GG, Boyle MM, Mirakhur RK. Probable histamine liberation with Atracurium. *Br J Anaesth.* 1985; 57 : 811 - 813.

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