HISTAMINE RELEASE AND CHANDONIUM IODIDE

Col YV SURI*, Dr BB NAYAK⁺,
Lt Col (Mrs) M JAIPRAKASH[#]

(Departments of Anaesthesiology, Pharmacology, and Pathology, Military Hospital (CTC) and Armed Forces Medical College, Pune)

ABSTRACT

Histamine releasing activity of chandonium iodide and *d*-tubocurarine was studied in guinea pig ileum (in vitro), guinea pig peritoneum (in vivo) and in human volunteers (in vivo) by intradermal testing at dilutions of 1:1,000 and 1:10,000 of the clinical dosage of drugs. *d*-tubocurarine revealed significant histamine releasing activity in in vivo animal experiments and high incidence of positive intradermal reaction, 53.5 per cent and 13.5 per cent, in human volunteers. Chandonium iodide neither showed histamine releasing activity in animals nor in man. In clinical terms, chandonium iodide appears to be a safe neuromuscular blocking agent.

MJAFI 1996; 52 : 245-247

KEY WORDS : Neuromuscular blocking agent; Histamine releasing activity; Chandonium iodide.

Introduction

Chandonium iodide (17 α - methyl, 1-3 β - pyrrolidino - aza-D-homo-5 androstene dimethiodide) is a new non-depolarizing neuromuscular blocking agent. Many neuromuscular blocking agents cause histamine release and adverse cardiovascular responses. In India, *d*-tubocurarine was known to cause mortality or morbidity but it has been replaced by pancuronium. New neuromuscular blocking agents having histamine releasing activity may not become popular in clinical anaesthesia. Therefore, experimental clinical pharmacology studies were conducted in animals and man to find out histamine releasing activity of chandonium iodide and its potential in clinical anaesthesiology.

Material and Methods

Animal Study: Guinea pigs of either sex (male 15, female 20) between 250-500 g weight were used in two sets of experiments:

(a) In vitro experiments: Pieces of terminal portion of ileum from stunned guinea pigs were mounted in Detes isolated organ bath containing a modified Tyrode's solution at 37°C. Spasmogenic activity of chandonium iodide at a bath concentration of 1 mg/mL was studied. Influence of chan-

donium iodide on acetylcholine chloride (0.0125×10^{-8} g/mL), and histamine dihydrochloride (0.06×10^{-8} g/mL) induced smooth muscle spasm were recorded.

(b) In vivo experiments: Guinea pigs were administered 100 mg/kg of chandonium iodide and *d*-tubocurarine intra-peritoneally. Animal behaviour of neuromuscular block was observed. From stunned guinea pigs, peritoneum was dissected, fixed on the slide and stained with 1 per cent toluidine blue and 1 per cent light green to study the architectural pattern and degranulation of mast cells. Ratio of the number of degranulated to normal cells was seen under high power microscope. Degree of degranulation of the mast cells was correlated to the histamine releasing activity of the drug.

Human Study: A total of 30 male volunteers, 15 each for chandonium iodide and *d*-tubocurarine, who gave informed consent were subjected to 0.2 ml of 1:1,000 and 1:10,000 dilution of intradermal injection. Criteria of a positive reaction [1] was described as a weal 1 cm or greater in diameter, persisting for more than 30 minutes, with or without associated clinical anaphylactoid reactions. Those who were predisposed to allergy were excluded from the study. None of them had been

*Senior Adviser (Anaesthesiology), Command Hospital Western Command, Chandimandir; ⁺Professor of Pharmacology, Armed Forces Medical College, Pune 411040; [#]Classified Specialist, Command Hospital Central Command, Lucknow.

administered anaesthesia in the past.

Results

Chandonium iodide did not have any spasmogenic activity at a bath concentration of 1 mg/mL. It did not produce any contraction of the smooth muscle of the ileum. In concentrations ranging from 0.1 to 1.0 mg/mL in the bath, it blocked the responses to acetylcholine. There was no change in the response to histamine but that of serotonin was potentiated at higher bath concentrations of 1.0 to 10.0 mg/mL (Table 1).

TABLE 1
Effect of chandonium iodide on isolated guinea pig ileum

Concentration of chandonium iodide (mg/mL)	Block of spasm induced by		
	Acetylcholine	Histamine	Serotonin
0.10	53	0	0
0.25	54	0	0
0.50	47	0	0
1.00	50	0	16*
5.00	—	Not done	37*
10.00	—	Not done	80*

* indicates potentiation

In the in vivo experiments, chandonium iodide produced a more rapid onset of muscular relaxation (8.3 ± 2.81 min) than *d*-tubocurarine (11.68 ± 4.15 min). Animal behaviour clearly indicated the paralysis of the limbs causing inability to move around on the table.

Lower dosages, 10-15 µg/kg of chandonium iodide, did not produce cellular degranulation whereas *d*-tubocurarine produced mild to moderate changes in both degranulation and/or loss of cellular pattern of mast cells (Table 2).

TABLE 2
Guinea pig peritoneum : Number of degranulated cells after administration of chandonium iodide and *d*-tubocurarine

Concentration of muscle relaxant	Number of degranulated cells/HPF		
Control	6.13	±	0.56
Chandonium iodide (100 µg/kg)	27.75*	±	12.35
<i>d</i> -tubocurarine (100 µg/kg)	77.61**	±	28.55

(* $p < 0.05$, ** $p < 0.001$ compared to control)

Human intradermal testing with chandonium iodide

Chandonium iodide did not produce positive intradermal reaction with 1:1,000 or 1:10,000 concentration of the drug. Those volunteers who received *d*-tubocurarine showed positive intradermal reaction in 8 (53.5%) and 2 (13.5%) individuals with 1:1,000 and 1:10,000 concentrations of the drug respectively. Positive reactions were not associated with hypotension, tachycardia, bronchospasm or any systemic manifestations.

Discussion

Many anaesthetic drugs cause high incidence of cutaneous reactions. *d*-tubocurarine, in addition, produces adverse cardiovascular responses. In India, *d*-tubocurarine has almost been replaced by pancuronium except in situations where hypotension may be desirable. New neuromuscular blocking agents having histamine releasing activity may not become popular in clinical anaesthesia.

Histamine is largely contained in the fixed mast cells and circulating basophils of the blood. Direct action of drugs and other chemicals upon cell surface receptors cause release of histamine which is the basis of its estimation in various animal models. However, it may also be facilitated by immune reaction (IgE), complement activation and by the presence of immune complexes.

Histamine action on smooth muscle causes vasodilatation, facilitates the movement of phagocytic cells across the tissues to their site of action and is an important "chemical" effector of the inflammatory response. The release of 1-2 ng/mL is sufficient to generate mild clinical manifestation [1] but at this concentration wide individual tolerance to histamine become apparent. Thirty per cent population as a whole are capable of releasing such small quantities of histamine (1-2 ng/mL) in response to a wide range of substances administered intravenously. Such release may be self-limiting and not indicative of a tendency to release harmful amounts of histamine in that individual upon further stimulus. At concentrations greater than 30 ng/mL plasma, life threatening situations are almost certainly present.

Histamine release by neuromuscular blocking agents

Neuromuscular blocking agents, like many other drugs, when administered repeatedly may induce sensitization to produce hypersensitivity response. Histamine causing systemic reactions may be initiated by the formation of aggregates (aggregate anaphylaxis) of mixed precipitated drugs, with or without plasma proteins, probably due to the failure to wash-out indwelling cannula between the administration of different drugs. This may be facilitated by cutaneous histamine release even to the needle response [2]. Therefore, aggregate anaphylaxis can be prevented by saline washings between the drugs used intravenously [2]. Intravenous anaesthetics may have additive effect with neuromuscular blocking drugs on the quantity and duration of action of the released histamine to produce clinical manifestations of anaphylactoid reaction. Histamine releasing activity of various neuromuscular blocking agents [3] may be compared with *d*-tubocurarine (Table 3).

TABLE 3
Comparison of histamine-releasing activity of neuromuscular blocking agents

Neuromuscular blocking agent	Relative histamine-releasing activity
<i>d</i> -tubocurarine	1.0
Atracurium	0.75
Fazadinium	0.50
Gallamine	0.33
Pancuronium	0
Vecuronium	0
Chandonium iodide	0

Fisher reported usefulness of intradermal testing of various anaesthetic agents to predict the adverse systemic reaction [4]. Robertson and co-workers [5] studied the responses in volunteers to intradermal injections of diluted atracurium, *d*-tubocurarine and vecuronium. High incidence of weals and flare reactions was observed with *d*-tubocurarine and atracurium but not to vecuronium. Similarly, Wood et al reported high incidence of positive "intradermal" weal and flare at dilutions of 1:1,000 of *d*-tubocurarine and atracurium [3]. Ansari et al [6] reported significant

increase in blood histamine levels with fall in blood pressure. Plasma histamine concentrations could be correlated with changes in heart rate and arterial pressure [7]. Gangopadhyay et al [8] confirmed the release of histamine in the blood with *d*-tubocurarine associated with fall in blood pressure whereas pancuronium produced marginal increase in blood histamine levels with insignificant changes in haemodynamics. Virendra and Taneja [9] showed clinical evidence of histamine release with 0.5 mg/kg atracurium whereas pancuronium did not show any propensity of histamine releasing activity. Our study has revealed an incidence of 53.5 per cent and 13.5 per cent positive intradermal reactions with *d*-tubocurarine at dilutions of 1:1,000 and 1:10,000 of the clinical dosage of the drug respectively. Positive intradermal reaction was not detected with chandonium iodide.

REFERENCES

1. Lorenz W, Doenicke A, Schoning B, Ohmann C, Grote D, Neugebauer E. Definition and classification of the histamine release response to drugs in anaesthesia and surgery. Studies in the conscious human subjects. *Klin Wochenschr* 1982; 60: 896-901.
2. Watkin J. Mechanisms and factors predisposing towards adverse response to intravenous anaesthetic substances. In: Thoroton JA, editor. *Adverse reaction of anaesthetic drugs*. Amsterdam: Elsevier 1985; 137-8.
3. Wood M, Watkin J, Wild G, Levy CJ, Harrington C. Skin testing in the investigations of reactions to IV anaesthetic drugs. A prospective trial of atracurium and *d*-tubocurarine. *Ann Franc Anaesth Reanim* 1985; 4: 176-7.
4. Fisher M. Intradermal testing after anaphylactoid reaction to anaesthetic drugs. Practical aspects of performance and interpretations. *Anaesth Intens Care* 1984; 12: 115-6.
5. Robertson EN, Boon LHD, Fragen RJ, Crul JT. Intradermal histamine release by 3 muscle relaxants. *Acta Anaesthesiol Scand* 1983; 27: 203-8.
6. Ansari G, Lal A, Gambhir SS. Histamine release with *d*-tubocurarine and atracurium. *Indian Journal of Anaesthesia* 1988; 36: 131-6.
7. Moss J, Rosow CK, Saverese JJ, Philbin BM, Kniffen KJ. Role of histamine in hypotensive action of *d*-tubocurarine in human. *Anesthesiology* 1981; 55: 19-22.
8. Gangopadhyay AN, Sharma P, Lal A. Histamine release with *d*-tubocurarine and pancuronium. *Indian Journal of Anaesthesia* 1986; 34: 91-5.
9. Virendra V, Taneja R. Comparison of cardiovascular effects of atracurium and pancuronium during clinical anaesthesia. *Indian Journal of Anaesthesia* 1990; 38: 211-5.