

Hemodynamic Effects of Muscle Relaxants a Comparative Study between Pancuronium and Vecuronium

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ABSTRACT:

BACKGROUND:

The cardiac effects of equipotent doses of pancuronium and vecuronium were compared in 50 patients, anaesthetized with thiopentone and maintenance with halothane. Heart rate and arterial pressure were recorded from simultaneous tracings of ECG and pulse oximeter and automatic noninvasive monitor respectively. Pancuronium (0.08 mg/kg) caused a significant increase in heart rate and significant changes in arterial pressure. The equipotent dose of vecuronium (0.08 mg/kg) caused no significant changes in heart rate and arterial pressure.

OBJECTIVE:

The study was designed to determine the comparison between Pancuronium Bromide & Vecuronium Bromide according to cardiovascular effects in young adult patients undergo different variety of surgical operation under general anaesthesia.

METHODS :

Fifty adult patients (ASA class I and II) were allocated to 2 subgroups: Group A (n=25) received pancuronium bromide 0.08mg/Kg and Group B (n=25) received vecuronium bromide 0.08mg/Kg. Anaesthesia was induced with Fentanyl (1µg/Kg), Sodium thiopentone (4-6mg/Kg) and maintained with Halothane 1% in Oxygen. The neuromuscular blocking agents were given and after 5-7 minutes tracheal intubation was performed with ease in all patients. Heart rate and mean arterial pressure were recorded every 10 minutes in all patients for 40 minutes.

RESULT:

There was significant differences in mean heart rate and mean arterial blood pressure in group A ($p < 0.05$). There was no significant differences in mean heart rate and mean blood pressure in group B ($p < 0.05$).

CONCLUSION:

From this study, it can be concluded that:

- 1- The use of pancuronium as a muscle relaxant cause significant increase in heart rate and mean blood pressure in anaesthetized patients.
- 2- The use of vecuronium as a muscle relaxant cause insignificant changes in heart rate and mean blood pressure in anaesthetized patients that lead us to prefer vecuronium on pancuronium for hemodynamic stability.

KEYWORD: pancuronium, vecuronium, fentanyl, thiopentone, halothane.

INTRODUCTION:

A rapid onset of action, allowing early tracheal intubation, is a desirable feature of neuromuscular blocking drug, since it should decrease the risk of the aspiration of gastric content. Suxamethonium has this property, but has, unfortunately, number of undesirable side effects. Vecuronium is a relatively intermediate-action non-depolarizing agent which has a

relatively slow onset time (time from administration to 90 or 100% blockade).⁽¹⁾ Pancuronium is a long-acting non-depolarizing agent, the time of onset is too slow to recommend its use to facilitate tracheal intubation.⁽²⁾ Anaesthetic drugs without deleterious cardiovascular effects are considered ideal, and are preferred in patients with poor cardiovascular reserve.⁽³⁾

Physiology of neuromuscular transmission:

The transmission of impulses from nerve to muscle is mediated by Acetylcholine, released by depolarization of nerve terminal. Acetylcholine

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diffuses across the junctional cleft and acts upon the post-junctional nicotinic receptors. Stimulation of these receptors triggers the excitation–contraction coupling sequence of the muscle. Acetylcholine is hydrolyzed in the synaptic cleft by the enzyme acetylcholinesterase.⁽⁴⁾ A medullated motor nerve fibre loses its myelin sheath when it reaches a striated muscle fibre. Each

terminal branch lies in a groove of the muscle fibre junctional cleft, forming the neuromuscular junction. Thus the nerve terminates at the 'pre-synaptic membrane', which is separated by a 'junctional/ synaptic cleft' from the 'post synaptic membrane' of the muscle (figure 1).⁽⁵⁾

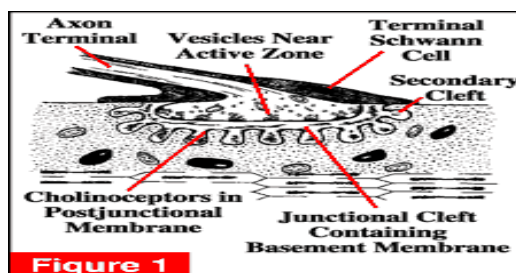


Figure 1 : Neuromuscular Junction.

Pancuronium remains one of the few muscle relaxants logically and rationally designed from structure-action relationship data. A steroid skeleton was chosen because of its appropriate size and rigidity. Acetylcholine moieties were inserted to increase receptor affinity. Although having many unwanted side-effects, a slow onset of action and recovery rate it was a big success and at the time the most potent neuromuscular drug available. Pancuronium and some other neuromuscular blocking agents block M^{ν} -receptors and therefore affect the vagus nerve, leading to hypotension and tachycardia. This muscarinic blocking effect is related to the acetylcholine moiety on the A ring on pancuronium. Making the N atom on the A ring tertiary, the ring loses its acetylcholine moiety, and the resulting compound, vecuronium, has nearly 100 times less affinity to muscarinic receptors while maintaining its nicotinic affinity

and a similar duration of action. Vecuronium is, therefore, free from cardiovascular effects.⁽³⁾ Non-depolarizing agents: A decrease in binding of acetylcholine leads to a decrease in its effect and neuron transmission to the muscle is less likely to occur. It is common understanding that non depolarizing agents block by acting as reversible competitive inhibitors. That is they bind to the receptor as antagonists and that leaves fewer receptors available for acetylcholine to bind to.^(1,4)

Pancuronium Bromide :

Pancuronium is characterized by the presence of two acetyl ester groups on the A and D rings of the steroidal molecule. fig. 2. Pancuronium is a potent neuromuscular blocking drug with both vagolytic and butyrylcholinesterase-inhibiting properties. Deacetylation of the 3-OH or 17-OH groups decreases its potency.⁽⁶⁾

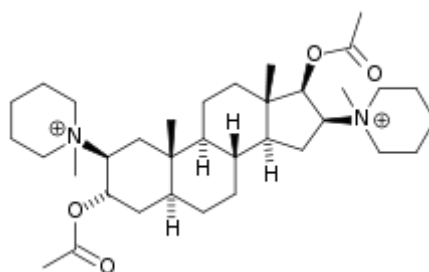


Figure 2 : Structural formula of pancuronium bromide.

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Pancuronium is cleared largely by the kidney⁽⁴⁾. Pancuronium typically produces a modest 10% to 15% increase in heart rate, mean arterial pressure, and cardiac output. The increase in heart rate reflects pancuronium induced selective blockade of cardiac muscarinic receptors (atropine-like effect), principally in the sinoatrial node. Histamine release and autonomic ganglion blockade are not produced by pancuronium⁽¹⁰⁾. Pancuronium causes a moderate increase in heart rate and, to a lesser extent, in cardiac output, with little or no change in systemic vascular resistance. Pancuronium induced tachycardia has been attributed to:

1- vagolytic action, probably secondary to inhibition of M₂ receptors,

2- sympathetic stimulation that involves both direct (blockade of neuronal uptake of norepinephrine) and indirect (release of norepinephrine from adrenergic nerve endings) mechanisms.⁽¹¹⁾ In studies in humans, Roizen and colleagues surprisingly found decreases in plasma norepinephrine levels after the administration of either pancuronium or atropine. They postulated that the increase in heart rate or rate-pressure product occurs because pancuronium (or atropine) acts through baroreceptors to reduce sympathetic outflow⁽¹²⁾. More specifically, the vagolytic effect of pancuronium increases the heart rate and, hence, blood pressure and cardiac output, which in turn influences the baroreceptors to decrease sympathetic tone. Support for this concept is

provided by the fact that prior administration of atropine will attenuate or eliminate the cardiovascular effects of pancuronium⁽¹³⁾. However, a positive chronotropic effect that places emphasis on the vagolytic mechanism has not been found in humans.⁽¹⁴⁾ During halothane anesthesia Edwards and associates observed a rapid tachycardia (more than 100 beats/min) that progressed to atrioventricular dissociation in two patients anesthetized with halothane who also received pancuronium. The only other factor common to these two patients was that both were taking tricyclic antidepressant agents. The magnitude of heart rate increase evoked by pancuronium seems more dependent on the pre-existing heart rate than the dose of the drug administered. The modest increase in blood pressure following the administration of pancuronium reflects the effect of heart rate on cardiac output in the absence of changes in peripheral vascular resistance. Cardiac stimulation effect of pancuronium may also increase the incidence of myocardial ischemia in patients with coronary artery disease. Histamine release and autonomic ganglion blockade are not produced by pancuronium⁽¹⁵⁾. Tachycardia is usually a side effect of pancuronium because of ganglionic stimulation and vagolysis⁽¹⁶⁾.

Vecuronium Bromide:

Vecuronium is the N-demethylated derivative of pancuronium in which the 2-piperidine substituent is not methylated (i.e., vecuronium lacks the N-methyl group at position 2) fig. 3.

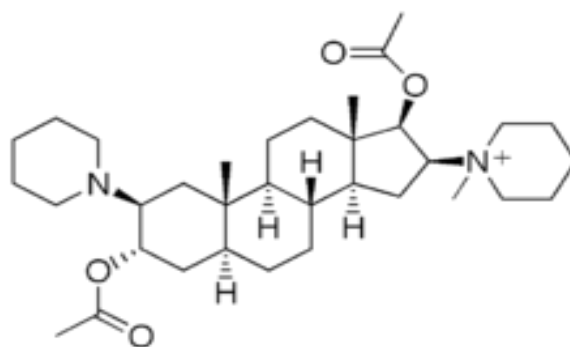


Figure 3 : Structural formula of vecuronium bromide.

At physiologic pH, the tertiary amine is largely protonated, as it is in dTc. The minor molecular modification relative to pancuronium results in:
1- a slight change in potency; 2- a marked reduction in vagolytic properties; 3- molecular

instability in solution, which explains in part the shorter duration of action of vecuronium than pancuronium; and 4- increased lipid solubility, which results in greater biliary elimination of vecuronium than pancuronium⁽¹⁷⁾. Vecuronium

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is typically devoid of circulatory effects, emphasizing its lack of vagolytic effects (pancuronium) or histamine release (atracurium).⁽¹⁷⁾

Several case reports have described the occurrence of severe bradycardia and even asystole after the administration of vecuronium. All of these cases were also associated with opioid administration. Subsequent studies indicated that administration of vecuronium alone does not cause bradycardia.⁽¹⁸⁾ When combined with other drugs that do cause bradycardia (e.g., fentanyl), however, the nonvagolytic relaxants such as vecuronium, cisatracurium, and atracurium allow this

mechanism to occur unopposed. Thus, the moderate vagolytic effect of pancuronium is often used to counteract opioid-induced bradycardia. All neuromuscular blocking drugs can cause noncompetitive inhibition of histamine-N-methyltransferase, but the concentrations required for such inhibition far exceed those that would be used clinically, except in the case of vecuronium, with which the effect becomes manifested at 0.1 to 0.2 mg/kg.⁽¹⁹⁾

The lack of cardiovascular side-effects and absence of histamine release make this the drug of choice for patients with autonomic and cardiac instability. Of all the neuromuscular blocking drugs available, vecuronium is the most specific for the neuromuscular junction, and therefore has the least side-effects.⁽²⁰⁾

Table A: Comparative Pharmacology of Long-Acting and Intermediate-Acting Non-depolarizing Muscle Relaxant.

Drug	Pancuronium	Vecuronium
ED ₅₀ (mg/kg)	0.07	0.05
Onset of maximum twitch depression(min.)	3.0	3.0
Recovery to 50% of control twitch height(min.)	40-70	20-30
Renal excretion (% unchanged)	80	10-20
Biliary excretion (% unchanged)	0-10	40-60
Hepatic degradation(%)	10-40	20-30
Hydrolysis in plasma	No	No

Fentanyl :

It is type of opioid analgesics, which is chemically related to mepiridine, has 100-fold the analgesic potency of morphine and is used in anaesthesia. The drug is highly lipophilic and has a rapid onset and short duration of action (10 to 20 minutes).

Sodium Thiopentone:

Thiopental is a potent anaesthetic but a weak analgesic. It is an ultrashort acting barbiturate and has a high lipid solubility. When administered intravenously, it quickly enters the CNS and depress function, often in less than 1 minute.

Halothane:

It is 2-Bromo-2-chloro-1,1,1-trifluoroethane. Its use rapidly spread because of its greater potency, ease of use, non-irritability and non-inflammability compared with diethyl ether and cyclopropane.⁽²¹⁾

PATIENTS AND METHODS:

In double blind study, fifty patient of ASA I or II of both sexes were allocated randomly in two groups, aged 18-40 (32, 8±8, 8) years and weight range between 50-80 (64, 3±6, 2) Kg.

All patients were underwent elective procedures, had no cardiovascular, neuromuscular, hepatic or renal disease, and were not receiving any drugs known or suspected of interfering with pulse rate or blood pressure. A consent was obtained from all patients.

Patients were allocated randomly to two groups, of 25 patients each, according to the muscle relaxant they received, as the following :-

Group A : each patient received 80 µg /Kg pancuronium.

Group B : each patient received 0.0 µg /Kg vecuronium.

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All patients were premedicated with midazolam (1-2mg) intravenously in both groups. Patients were preoxygenated with 100% oxygen for three minutes then Anaesthesia was induced with Fentanyl 1µg /Kg and sodium thiopentone 4-6 mg /Kg intravenously. Non depolarizing muscle relaxant was administered intravenously (as described above) to facilitate tracheal intubation. When paralysis had been obtained the trachea intubated and the lungs ventilated mechanically.

Anaesthesia was maintained with halothane 1% in oxygen. The heart rate and mean arterial pressure were recorded by using pulse oximeter and automatic non-invasive monitor (Kontron), respectively. The heart rate (HR) and mean arterial pressure (MAP) were measured before induction, and at interval following the administration of non-depolarizing agents (with onset 1 minute) as baseline and each 10 min. after tracheal intubation.

The trachea was not intubated until with onset (1min.) reading was taken, in order to avoid effect of intubation on the cardiovascular system.

RESULTS:

The study group included 19 male and 31 female patients with a mean age 32.7 (SD 6.6) years (range 18-45 years) and a mean weight of 74.2 (SD 10.0) kg (range 50-100kg). Patient data for group A and B are shown in table I and II respectively. Characteristic of each group are summarized in table III. The mean ages and weight of the patients in the two groups did not differ significantly ($p < 0.05$). Cardiovascular data are presented in table IV and V (also the result are shown in figures 1,2). They show the pre-induction cardiovascular indices, with onset and each 10 minutes after tracheal intubation for patients who received each individual drugs separately. There were significant differences in mean heart rate and significant differences in mean arterial blood pressure in group A ($p < 0.05$). There was no significant differences in mean heart rate and mean blood pressure in group B ($p < 0.05$). t-test was used to determine the significance of differences between groups. The null hypothesis was rejected at $p < 0.05$. All results are expressed as mean (as an index of central tendency) with the standard deviation or range as the indexes of dispersion.

Table III : Patients and demographic data, mean ± SD (range).

Group	A	B
No. of patient	20	20
Gender (male:female)	10:10	9:11
Age(years)	32.7(9.1) (18-45)	32.2(8.0) (18-45)
Weight(kg)	74.2(9.8) (50-100)	73.7(10.9) (50-100)

Table (IV): Mean Heart Rate(HR) (beat/min.) (mean ± SD).

Time	Group A	Group B
Pre-induction	90.3 (10.0)	92.0 (9.3)
With onset 1min.	109.8 (11.9)	90.0 (8.7)
Time after Intubation (min.)		
10 min.	98.0 (11.7)	91.3 (10.3)
20 min.	96.2 (11.6)	89.0 (8.4)
30 min.	94.1 (9.7)	88.0 (8.1)
40 min.	94.0 (12.2)	92.0 (9.3)

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Mean heart rate
(beats/min.)

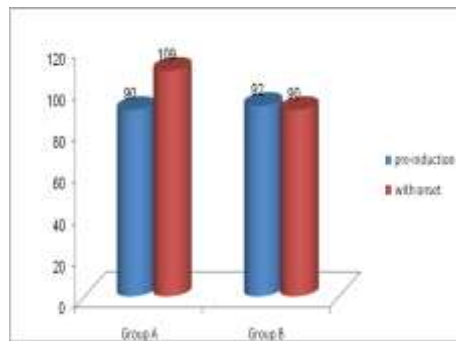


Figure 4 : Comparison of the mean heart rate(beats/min).

Mean arterial pressure
(mmHg)

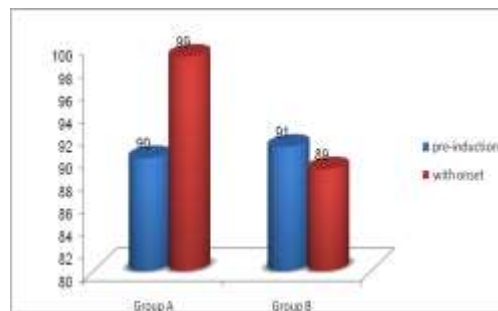


Figure 5: Comparison of the mean blood pressure(mmHg)

DISCUSSION:

The cardiovascular effects of pancuronium are well recognized: it has been shown to induce small increases in HR, CO and MAP, but these have been regarded as at worst acceptable or at best a positive advantage, countering any tendency for these variables to decrease as anaesthesia is induced. The causes of these effects are thought to be a combination of post-ganglionic vagal blockade and the blocking of noradrenaline re-uptake. Although the changes in HR seen with pancuronium may be marked in certain patients, the lack of histamine release and of ganglionic blockade have ensured its popularity in cardiovascular anaesthesia. In a comparison of a variety of non-depolarizing neuro-muscular blockers, they reported no significant cardiovascular changes with vecuronium, in contrast to the significant increases in HR and MAP found with pancuronium. Vecuronium, with its shorter duration of action and lack of cardiovascular stimulation, offers significant advantages over

pancuronium. The wide margin of safety between the clinical dose and that producing significant cardiovascular side effects, allows the initial dose of the drug to be increased to give a duration of action comparable to that of pancuronium, should this be desired, without any tendency to develop side effects. Although the idea of a neuromuscular blocking drug without cardiovascular side effects is attractive, its use may result in heart rates that are slower than many anaesthetists consider acceptable. Many of the non-depolarizing neuromuscular blocking agents in clinical use are known to produce autonomic side-effects, blockade of cardiac muscarinic receptors and blockade of the re-uptake of noradrenaline at cardiac sympathetic nerve terminals being possible mechanisms of action. Studies in animals and in man have suggested that vecuronium, a monoquaternary analogue of pancuronium, is without such autonomic side-effects. The purpose of this study was to compare the cardiac effects of equipotent

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doses of vecuronium and pancuronium during halothane anaesthesia⁽¹¹⁾ These results indicate that vecuronium had minimal effects on HR and MAP of the normal heart. The equipotent doses of the two drugs administered in this study correspond to 1,2 times the 90% blocking dose. They administered vecuronium in doses up to three times ED₉₀ and found that HR was stable and that there were no significant changes in arterial pressure. The changes in HR and MAP following injection of pancuronium are similar to the findings of other workers. However, pancuronium is known to facilitate sympathetic cardiac ganglion transmission and block the re-uptake of noradrenaline at cardiac sympathetic nerve terminals. Recently they described a possible direct positive inotropic effect mediated by beta-adrenergic receptor stimulation. In contrast, vecuronium caused only minimal changes in heart rate and blood pressure. The apparent lack of inotropic effect of vecuronium is in accordance with the in vitro studies of Marshall and Ojewole, and Docherty and McGrath,. Their results indicated that vecuronium is approximately 30 times less active than pancuronium in potentiating cardiac sympathetic transmission and that vecuronium, in contrast to pancuronium, does not inhibit the neuronal reuptake of noradrenaline⁽¹¹⁾ In summary, our data indicate that vecuronium administered in a dose 1,2 times the 90% blocking dose is without effect on cardiac performance in patients with normal cardiovascular function.

CONCLUSION:

From this study, it can be concluded that:

1-The use of pancuronium as a muscle relaxant cause significant increase in heart rate and mean blood pressure in anaesthetized patients. 2- The use of vecuronium as a muscle relaxant cause insignificant changes in heart rate and mean blood pressure in anaesthetized patients that lead us to prefer vecuronium on pancuronium especially in patients with hemodynamic instability.

RECOMMENDATIONS

Although the non-depolarizing drugs are in daily use by the anesthetists in our country but there is a deficiency in some important types, so we advise to provide the operation rooms with vecuronium continuously to avoid undesirable events which may meet the anesthetists

especially in patients with cardiovascular impairment.

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