Large doses of vecuronium and plasma histamine concentrations

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The authors studied 20 surgical patients to determine the effect of large doses of vecuronium on plasma histamine concentrations. Patients were unpremedicated and anaesthetized with nitrous oxide and halothane via a mask. Tracheal intubation was performed without the use of muscle relaxants. Fifteen min later and before surgery had begun, vecuronium, in doses of 0.1 and 0.2 mg · kg^{-1} (n = 10 for each dose), was administered as an IV bolus. Arterial blood samples were obtained prior to and 2, 5, and 10 min after vecuronium administration and analyzed for plasma histamine by a radioenzymatic method. Arterial blood pressure and heart rate were measured continuously. In one patient who received 0.1 mg · kg^{-1} of vecuronium, plasma histamine concentrations at 2 min were 275 per cent of the control histamine value but fell below control at 10 min. This increase in plasma histamine was not associated with clinically important changes in blood pressure or heart rate. As a group, study patients had no significant changes in plasma histamine concentrations with either dose of vecuronium. In addition, mean plasma histamine values for each sampling interval did not differ between the two patient groups. Mean arterial blood pressure (MAP) decreased significantly at 10 min in patients receiving vecuronium 0.1 mg · kg^{-1}, and at 2 and 10 min in patients receiving 0.2 mg · kg^{-1} of vecuronium. However, these decreases in MAP were not clinically important. Changes in plasma histamine concentrations did not correlate with corresponding changes in MAP. Heart rate did not change significantly in any patient during the study. The authors conclude that vecuronium can be given in doses up to 0.2 mg · kg^{-1} to facilitate tracheal intubation without significant changes in cardiovascular status, but with rare increases in plasma histamine concentrations.

Key words

BLOOD PRESSURE: measurement; HEART: pulse rate; HISTAMINE: assay; NEUROMUSCULAR RELAXANTS: vecuronium.

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Supported by a grant from Organon Pharmaceuticals.

Administration of vecuronium, in doses of 0.2 mg · kg^{-1} intravenously, has been recommended to facilitate rapid intravenous inductions of anaesthesia.[1] Though previous investigators have shown minimal changes in plasma histamine[2] and arterial blood pressure[3] with such high doses of vecuronium, there are several reports of hypotension and possible histamine release from vecuronium in surgical patients.[4–6] Clayton *et al.* reported a body-wide rash in response to vecuronium administration in an atopic seven-year-old boy.[4] A similar rash with hypotension was observed in a 40-year-old female who had received 6 mg of vecuronium as an IV bolus.[5] Bronchospasm was noted in a 66-year-old man after each administration of vecuronium (three separate doses) by O'Callaghan *et al.*[6] We therefore proposed to study the ability of large intravenous doses of vecuronium to increase plasma histamine concentrations and to alter heart rate and mean arterial blood pressure.

Methods

We studied 20 patients scheduled for elective surgical procedures who had given an informed consent as approved by the University of California Committee on Human Research. Patients were unpremedicated and had not received antihistaminic drugs in the week prior to surgery. Anaesthesia was induced with 60 per cent nitrous oxide and increasing concentrations of halothane via a mask; thiopentone 2 mg · kg^{-1} IV was given only if needed to facilitate the induction of anaesthesia. Tracheal intubation was performed without the use of muscle relaxants.

Ventilation was controlled to maintain $PaCO_2$ in a range of 35–40 mmHg. Anaesthesia was continued with halothane, 0.7 per cent end-tidal, and 60 per cent nitrous oxide in oxygen, as measured by mass spectrometry. A radial artery catheter was inserted to allow continuous monitoring of blood pressure and heart rate.

Patients were then randomly assigned to receive vecuronium at a dose of 0.1 or 0.2 mg · kg^{-1} IV (n = 10 for each). When stable anaesthetic conditions had been maintained for at least 15 min and before the surgical procedure began, vecuronium was administered as a rapid IV bolus. Arterial blood samples were obtained prior to and 2, 5 and 10 min after vecuronium administration.

Samples were immediately heparinized, cooled, and the plasma harvested. Plasma samples were stored at −70° C until histamine concentrations were determined by a radioenzymatic assay.[7] All samples were assayed in duplicate with duplicate internal standards. Intra- and inter-assay variation was less than ten per cent, and the sensitivity of the assay was 20 $pg \cdot ml^{-1}$.

Data for plasma histamine, mean arterial blood pressure (MAP), and heart rate were statistically compared by repeated measures analysis of variance and compared to control values by Dunnett's test. Mean plasma histamine values for each sample period were compared between the two patient groups by paired t test. Statistical significance was accepted at $p < 0.05$. Correlation of changes in plasma histamine concentrations with corresponding changes in MAP was done graphically.

Results

Plasma histamine concentrations after a vecuronium bolus increased by more than ten per cent from control in four patients after 0.1 $mg \cdot kg^{-1}$ vecuronium and in three patients after 0.2 $mg \cdot kg^{-1}$ vecuronium (Table I). The largest increase was observed in patient #8, who received 0.1 $mg \cdot kg^{-1}$ of vecuronium. Data for plasma histamine for two patients [#4 in the 0.1 $mg \cdot kg^{-1}$ group (5 min value) and #10 in the 0.2 $mg \cdot kg^{-1}$ group (all values)] could not be included because of inability to measure the plasma histamine concentration. Mean values for plasma histamine concentrations showed no significant change with either dose of vecuronium. Mean plasma histamine values for each sampling period did not differ between the two groups.

Mean arterial blood pressure decreased at the 10 min sampling period in the 0.1 $mg \cdot kg^{-1}$ patient group, and at the 2 and 10 min periods in the 0.2 $mg \cdot kg^{-1}$ group (Table II). No patient experienced a decrease in MAP of greater than 15 per cent from control. Heart rate did not significantly change in either patient group.

Changes in MAP were correlated with changes in plasma histamine graphically (Figure). Points in the upper left hand quadrant of the graph suggest a correlation between decreases in MAP and increases in plasma histamine. Of 26 data points that could be defined to a specific quadrant of the graph for the 0.1 $mg \cdot kg^{-1}$ group, seven points were in the upper left hand quadrant. Two of these (at 2 and 5 min) were from patient #8 described above. For the 0.2 $mg \cdot kg^{-1}$ group, 24 points could be defined to quadrants, eight of which were in the upper left hand quadrant. Points in the lower left hand quadrant of this graph suggest a correlation between decreases in MAP and decreases in plasma histamine concentration. Nine of 26 data points for the 0.1 $mg \cdot kg^{-1}$ group were in this quadrant; 12 of 24 for the 0.2 $mg \cdot kg^{-1}$ group.

TABLE I Plasma histamine concentrations ($pg \cdot ml^{-1}$)*

	Minutes after vecuronium bolus			
Patient #	*0*	*2*	*5*	*10*
Dose = 0.1 $mg \cdot kg^{-1}$				
1	185	263 (42)	199 (7)	351 (89)
2	317	278 (−12)	228 (−28)	205 (−35)
3	263	314 (19)	496 (88)	661 (151)
4	193	180 (−7)	NA	238 (23)
5	193	193 (0)	134 (−30)	145 (−25)
6	376	384 (2)	532 (41)	670 (78)
7	187	103 (−45)	184 (−2)	145 (−22)
8	499	1871 (275)	1573 (215)	307 (−38)
9	174	186 (7)	189 (9)	146 (−16)
10	291	124 (−57)	152 (−48)	115 (−60)
Mean ± SD	268 ± 101	390 ± 528	410 ± 460	298 ± 208
Dose = 0.2 $mg \cdot kg^{-1}$				
1	229	279 (22)	330 (44)	228 (0)
2	109	115 (6)	74 (−32)	85 (−22)
3	118	137 (16)	139 (18)	460 (290)
4	267	219 (−18)	204 (−24)	190 (−29)
5	123	50 (−59)	47 (−62)	46 (−63)
6	309	75 (−76)	155 (−50)	240 (−22)
7	126	83 (−34)	148 (17)	107 (−15)
8	147	149 (1)	140 (−5)	119 (−19)
9	197	120 (−39)	208 (6)	124 (−37)
10	NA	NA	NA	NA
Mean ± SD	181 ± 73	136 ± 73	161 ± 82	178 ± 124

*Values in parentheses represent per cent change from control.
NA = not able to measure plasma histamine.

The two patient groups did not differ with respect to age (36.3 ± 7.0 years in the 0.1 $mg \cdot kg^{-1}$ group vs 37.1 ± 8.7 years for the 0.2 $mg \cdot kg^{-1}$ group (mean ± SD)) or weight (71.6 ± 14.1 kg vs 72.6 ± 16.9, respectively). Seven points in each group received thiopentone to facilitate induction of anaesthesia.

Discussion

Plasma histamine concentrations in unanaesthetized normal subjects using the radioenzymatic method are 303 ±

TABLE II Mean arterial pressure (MAP ± SD) and heart rate (HR ± SD)

	Minutes after vecuronium bolus			
	0	*2*	*5*	*10*
Dose = 0.1 $mg \cdot kg^{-1}$				
MAP (mmHg)	81 ± 13	80 ± 13	78 ± 14	77 ± 14*
HR ($beats \cdot min^{-1}$)	72 ± 18	70 ± 18	70 ± 16	69 ± 15
Dose = 0.2 $mg \cdot kg^{-1}$				
MAP (mmHg)	77 ± 15	74 ± 15*	75 ± 16	74 ± 12*
HR ($beats \cdot min^{-1}$)	72 ± 24	73 ± 21	74 ± 24	72 ± 22

* = different from control ($p < 0.05$).

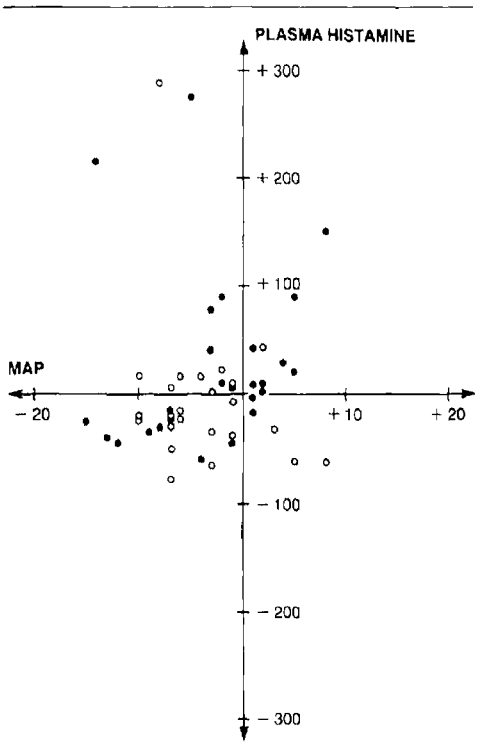

FIGURE Correlation of per cent change from control values for plasma histamine and mean arterial pressure (MAP) in patients after the administration of 0.1 mg·kg^{-1} (●) and 0.2 mg·kg^{-1} (○) of vecuronium.

81 (SD) pg·ml^{-1},[7] a value which is similar to the control plasma histamine concentrations we measured in anaesthetized subjects. Halothane anaesthesia, which was used in our study, has been demonstrated *in vitro* to reduce the release of histamine from human tissue.[8] However, Basta *et al.*,[2] studying patients under narcotic anaesthesia, also reported no significant changes in plasma histamine concentrations after vecuronium.

Measurement of plasma histamine can predict the cardiovascular effects of intravenous boluses of nondepolarizing muscle relaxants. For instance, Moss *et al.* found that a dose of d-tubocurarine of 0.75 mg·kg^{-1} produced such significant increases in plasma histamine concentrations and resultant hypotension in two patients that they precluded administering this high dose of d-tubocurarine to other patients. In contrast, our study has demonstrated the relative safety of increasing the dose of vecuronium from 0.1 mg·kg^{-1} to 0.2 mg·kg^{-1}, as recommended by Lennon *et al.*[1] to achieve rapid tracheal intubation. Vecuronium rarely produces direct release of large amounts of endogenous histamine (one out of 20 patients in our study), and certainly is less likely to produce histamine release than d-tubocurarine, metocurine or atracurium. However, nondepolarizing relaxants such as vecuronium can produce severe anaphylactoid reactions by means of a type I hypersensitivity reaction.[10,11] History of allergy, atopy, asthma, or a previous anaesthetic drug reaction may help identify patients at risk for developing this response to nondepolarizing relaxants, but in most cases the response is unpredictable. Thus, vecuronium, as with any intravenous drug, should be administered with caution, particularly in large intravenous doses, but with the knowledge that it does appear to be associated with very rare adverse reactions.

The absence of correlation between plasma histamine concentrations and MAP in our study agrees with the results of Cork *et al.*[12] who performed a study similar to ours using a dose of 0.12 mg·kg^{-1} vecuronium. They found no significant changes in plasma histamine concentrations or MAP, and linear regression analysis demonstrated no correlation between these two parameters. Atracurium, 0.5 mg·kg^{-1}, was also studied, and increases in plasma histamine and decreases in MAP were observed at each sampling interval, with significant correlation between changes in plasma histamine concentrations and MAP. Our results also suggest that there is no correlation between size of administered dose of vecuronium and changes in MAP, such as that demonstrated for d-tubocurarine[9] and atracurium.[13]

In summary, we conclude that vecuronium can be given in doses up to 0.2 mg·kg^{-1} to facilitate tracheal intubation without significant changes in cardiovascular status, but with rare increases in plasma histamine concentrations.

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Résumé

Les auteurs ont étudié 20 patients chirurgicaux afin de déterminer les effets de grandes doses de vécuronium sur les concentrations plasmatiques d'histamine. Les patients étaient non-prémédiqués et anesthésiés avec du protoxyde d'azote halothane au masque. L'intubation trachéale fut faite sans relaxant musculaire. Quinze minutes plus tard et avant le début de la chirurgie, du vécuronium à des doses de 0.1 et 0.2 mg · kg^{-1} (n = 10 pour chaque dose) a été administré en bolus intraveineux. Les échantillons sanguins artériels ont été obtenus avant et à 2, 5 et 10 minutes après l'administration de vécuronium et l'histamine plasmatique fut analysée par méthode radioenzymatique. La pression artérielle et la fréquence cardiaque furent mesurées continuellement. Les auteurs ont trouvé que chez un patient ayant reçu 0.1 mg · kg^{-1} de vécuronium, la concentration plasmatique d'histamine à deux minutes était de 275 pour cent du contrôle et diminuant après dix minutes plus bas que la valeur de contrôle. Cette augmentation de l'histamine plasmatique n'était pas associée à des changements importants cliniquement dans la pression artérielle et la fréquence cardiaque. Comme groupe les patients étudiés n'ont pas démontré de changement significatif dans les concentrations d'histamine plasmatique avec aucune des doses administrées. De plus, la valeur moyenne de l'histamine plasmatique pour chaque intervalle d'échantillonnage n'a pas montré de différence entre les groupes de patients. La pression artérielle moyenne (MAP) a diminué significativement à dix minutes chez les patients ayant reçu du vécuronium 0.1 mg · kg^{-1} et à deux et dix minutes chez les patients ayant reçu 0.2 mg · kg^{-1} de véruconium. Cependant cette diminution de la MAP n'avait pas d'importance clinique. Les changements de concentrations d'histamine plasmatique n'avaient pas de corrélation avec les changements de la MAP. La fréquence cardiaque n'a pas changé significativement chez aucun des patients durant l'étude. Les auteurs concluent que le vécuronium peut être donné jusqu'à des doses de 0.2 mg · kg^{-1} afin de faciliter l'intubation trachéale sans changement significatif de l'état hémodynamique et avec une rare augmentation de la concentration d'histamine plasmatique.