COMPARISON OF THE EFFECTS OF ORG NC45 AND PANCURONIUM BROMIDE ON HEART RATE AND ARTERIAL PRESSURE IN ANAESTHETIZED MAN

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SUMMARY

The effects of Org NC45 and pancuronium bromide on heart rate and arterial pressure were studied in anaesthetized man. A bolus of either Org NC45 0.12 mg kg\(^{-1}\) or pancuronium 0.1 mg kg\(^{-1}\) was administered to lightly anaesthetized unstimulated subjects. Following Org NC45 heart rate decreased in the majority of subjects (mean and SEM 3.78 \pm 1.36), whereas after pancuronium heart rate was increased (mean and SEM 11.91 \pm 1.9). The changes in mean arterial pressure observed were minimal. The effect of endotracheal intubation on mean arterial pressure was then studied. Increase of mean arterial pressure was observed in all subjects. The increase was more marked in those patients who had received pancuronium and was significantly higher than in those patients who had received Org NC45 (P<0.01). We conclude that Org NC45 is devoid of vagal blocking action, and that the difference in response to the stimulus of endotracheal intubation is a result of the different effects exerted on the sympathetic nervous system by Org NC45 and pancuronium.

Org NC45 was developed as a result of pharmacological tests on the neuromuscular and autonomic blocking actions of a series of pancuronium analogues. Org NC45 was selected because it possesses negligible ganglion blocking activity, and there is a wide margin between neuromuscular and vagal blocking doses (Marshall, Agoston et al., 1980). This suggested that Org NC45 would have minimal cardiovascular side-effects, in comparison with pancuronium.

Increases in heart rate following pancuronium have usually been attributed to blockade of cardiac muscarinic receptors (Saxena and Bonta, 1970). Org NC45 is 35 times less active than pancuronium in blocking cardiac responses to vagal stimulation in anaesthetized cats (Durant et al., 1979) and 500 times less potent than pancuronium in blocking the bradycardia produced by vagal stimulation in the pithed rat (Marshall, McGrath et al., 1980).

Org NC45 also differs from pancuronium in its effects on the sympathetic nervous system. It is four times less potent as an inhibitor of the neuronal uptake of noradrenaline (Uptake\(_{\text{NA}}\)) in the isolated perfused rat heart (Salt, Barnes and Conway, 1980). It is approximately 30 times less active than pancuronium in potentiating the effects of sympathetic cardioaccelerator stimulation in pithed rats and does not potentiate the cardiac effects of noradrenaline in guineapig atria (Marshall, McGrath et al., 1980).

METHODS

Fit adults gave informed consent to the study. Premedication consisted of diazepam 10 mg orally for those patients less than 70 kg in weight and 15 mg for those more than 70 kg and was administered 90 min before induction of anaesthesia. On arrival in the anaesthetic room a 22-gauge Teflon cannula (Abbocath) was inserted into the radial artery under local anaesthesia. This was connected via a pressure transducer (Hewlett-Packard 1280A) to a pen recorder (Brush Clevite). Anaesthesia was induced with thiopentone 5 mg kg\(^{-1}\) and maintained with 70% nitrous oxide in oxygen via a face-mask. Five minutes after the administration of thiopentone a bolus of either pancuronium 0.1 mg kg\(^{-1}\) (11 patients) or Org NC45 0.12 mg kg\(^{-1}\) (12 patients) was administered. Subjects were randomly assigned to these two groups.

When spontaneous ventilation ceased the lungs were ventilated artificially with 70% nitrous oxide in oxygen. Five minutes after the administration of

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the neuromuscular blocking drug a bolus of thiopentone 1.5 mg kg⁻¹ was administered and the trachea intubated. Mean arterial pressure (diastolic + [systolic – diastolic]/3) and heart rate were determined in the minute before the administration of the neuromuscular blocker. This represented the control values for individual subjects. Mean arterial pressure and heart rate in the 4th minute following injection of pancuronium and Org NC 45, and the peak mean arterial pressure on intubation, were determined.

RESULTS

Examples of the traces during the control period, the 4th min following injection of the neuromuscular blocking drug and the response to endotracheal intubation, are shown for two patients in the pancuronium series (fig. 1) and two patients in the Org NC 45 series (fig. 2).

Heart rate

The change in heart rate for all subjects was expressed as the percentage change of the control values (fig 3). In the subjects who received Org NC 45, heart rate was increased in two (2% and 4% of control), was unchanged in two and decreased in the remainder by up to 12% of control. In absolute terms the decrease was 3.78 ± 1.36 (mean ± SEM) and this was significantly different from the control values (P < 0.025, t test). In the subjects who received pancuronium the heart rate was consistently increased. The increase in heart rate ranged from 5% of control to 30% of control. In absolute terms the increase in heart rate was 11.91 ± 1.9

(mean ± SEM) and this was significantly different from the control values (P < 0.001, t test). There was a correlation between the increase in heart rate (expressed as percentage change of control) and the control heart rate (r = 0.635).

Mean arterial pressure

Mean arterial pressure in the minute before the administration of the two drugs was not significantly different in the two groups. The mean arterial pressure at the three relevant points in the study — control, the 4th min following injection of the drugs and the peak mean arterial pressure on intubation — are shown for pancuronium and Org NC 45 (fig. 4).

In the patients given pancuronium mean arterial pressure was increased in the majority (range -2.1% of control to +11.1% of control). This change in mean arterial pressure was significantly different from the control values (P < 0.025, t test). In the patients who received Org NC 45, mean arterial pressure decreased in some (maximum decrease 12% of control) and was increased in others (maximum 8.8% of control). There was no statistical significance between the values after injection of the drug compared with the control values (t test). Mean arterial pressure was increased in all subjects as a result of endotracheal intubation. There was, however, a significantly different response in peak mean arterial pressure on intubation in those patients who had received pancuronium and Org NC 45 (P < 0.01, t test and rank test). These changes in peak mean arterial pressure were expressed as percentage increase of control of each subject (fig. 5).
CARDIOVASCULAR EFFECTS OF ORG NC45 AND PANCURONIUM

DISCUSSION

The effect of a bolus dose of Org NC 45 on heart rate in lightly anaesthetized man is different from that of pancuronium. The dose of Org NC45 used in this trial appears to be devoid of the vagal blocking action observed with pancuronium. Animal studies which have shown Org NC45 to be devoid of vagal blocking activity (Booij et al., 1980; Durant, Houwfortjes and Cruyl, 1980), have been confirmed in man. The changes observed with pancuronium are consistent with previously reported work (Kelman and Kennedy, 1971; Miller, Eger and Stevens, 1975). When pancuronium is used in clinical practice, a stimulus that produces a sympathetic discharge results in tachycardia that would be more marked in the presence of vagal blockade. Excessive tachycardia may occur when pancuronium is used; this would be less likely to occur with Org NC45.

The effects of pancuronium and Org NC 45 on mean arterial pressure seemed to be dependent on the conditions prevailing at the time the data were collected. Org NC 45 did not have a consistent effect on mean arterial pressure after a bolus injection in the lightly anaesthetized unstimulated subject, and changes that did occur were minimal. The injection of pancuronium resulted in a small but significant increase in arterial pressure. This increase in mean arterial pressure did not appear to correlate with the increase in heart rate. Endotracheal intubation produced an increase in arterial pressure in all the subjects in this trial. There was, however, a difference in the pressor response to intubation between the two groups. The increase in mean arterial pressure during intubation after Org NC 45 was modest and consistent. The increase in mean arterial pressure in those patients who had received pancuronium was greater and tended to be inconsistent.

In this trial an attempt was made to produce a consistent level of anaesthesia at the time of endotracheal intubation, by the careful control of the doses of anaesthetic agents used and critical timing of the manoeuvres performed. Despite this it is

FIG. 3. Change in heart rate in the 4th min following injection of Org NC 45 and pancuronium, expressed as percentages of control values.

FIG. 4. Mean arterial pressure (mm Hg) during the control period, in the 4th min after injection of pancuronium 0.1 mg kg⁻¹ and Org NC45 0.12 mg kg⁻¹ and the peak readings on endotracheal intubation.
impossible to be sure that all patients were at the same level of anaesthesia for the standard stimulus of endotracheal intubation. It could be anticipated, however, that the variation in level of anaesthesia would be the same in the two groups.

An explanation for the observed results may be that Org NC45 and pancuronium exert different effects on the sympathetic nervous system. Pancuronium sensitizes the sympathetic nervous system by inhibiting the reuptake of noradrenaline into sympathetic nerves. A pressor response would not be anticipated following a bolus injection of the drug. Any change in arterial pressure in an unstimulated subject could be attributed to the mild tachycardia produced by vagal blockade, although this was not the case in this trial. In the presence of a sympathetic discharge, however, an augmented response would be expected. Org NC45 is unlikely to sensitize the sympathetic nervous system (Salt, Barnes and Conway, 1980), and one would not expect to see the exaggerated changes in mean arterial pressure during periods of sympathetic stimulation. This may explain why the two groups in this trial behaved in a similar fashion with respect to changes in mean arterial pressure after the drugs were administered, yet had a different response to endotracheal intubation.

The apparent discrepancies in the early experimental work on the cardiovascular effects of pancuronium in man (Baird and Reid, 1967; McDowell and Clark, 1969; Fastrer and Agoston, 1970; Kelman and Kennedy, 1971), may be a result of the different plans of study used and the difference in stimulation taking place during the studies, when the data were collected. In the study reported by Lyons and Clark (1972), four neuromuscular blocking drugs were studied — pancuronium, gallamine, alcuronium and tubocurarine. After injection of the drugs it was noted that pancuronium produced little change in mean arterial pressure. The fact that the greatest increase in arterial pressure in intubation 3 min after the injection of the drugs was seen with pancuronium did not receive comment.

The cardiovascular side-effects of any neuromuscular blocking drug will be dependent on the inherent pharmacological properties of the drug, and the depth of anaesthesia in relation to the surgical stimulus.

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REFERENCES


COMPARATION DES EFFETS DU ORG NC45 ET DU BROMURE DE PANCURONIUM SUR LA FREQUENCE CARDIAQUE ET LA PRESSION ARTERIELLE CHEZ L'HOMME ANESTHESIE

RESUME
Nous avons etudié les effets de l'Org NC45 et du bromure de pancuronium sur la fréquence cardiaque et la pression artérielle chez l'homme anesthésié. Une injection rapide de 0,12 mg kg⁻¹ d'Org NC45 ou de 0,1 mg kg⁻¹ de bromure de pancuronium a été faite à des sujets légèrement endormis, non stimulés. Après l'Org NC45, la fréquence cardiaque diminue chez la plupart des sujets (moyenne et ESM. 3,78 ± 1,76), tandis qu'elle augmente après pancuronium (11,91 ± 1,9). Les modifications de la pression artérielle moyenne observées sont minimes. On a ensuite étudié les effets de l'intubation endotrachéale sur la pression artérielle moyenne. Tous les sujets présentent une augmentation de la pression artérielle moyenne. Cette augmentation est plus marquée chez les sujets qui reçoivent du pancuronium, sujets chez qui elle est significativement plus importante que chez les sujets qui reçoivent de l'Org NC45 (P<0,01). Nous en concluons que l'Org NC45 est dénué d'action parasympatholytique et que la différence de réponse au stimulus de l'intubation endotrachéale est due aux effets différents exercés par l'Org NC45 et la pancuronium sur le système nerveux sympathique.

VERGLEICH DER WIRKUNG VON ORG NC45 UND PANCURONIUMBROMID AUF PULSFREQUENZ UND BLUTDRUCK BEIM ANASTHESIERTEN PATIENTEN

ZUSAMMENFASSUNG
Die Wirkung von Org NC45 und Pancuroniumbromid auf Pulsfrequenz und arteriellen Blutdruck wurde an anästhetisierten Menschen untersucht. Ein Bolus von entweder 0,12 mg kg⁻¹ Org NC45 oder 0,1 mg kg⁻¹ Pancuronium wurde Patienten gegeben, die sich in leichter Narkose befanden und auf den Reiz ausgiebisch reagierten. Nach Org NC45 nahm die Pulsfrequenz bei der Mehrheit der Patienten ab (Mittelwert und S. A. 3,78 ± 1,36), während sie nach Pancuronium zunahm (Mittelwert und S. A. 11,91 ± 1,9). Die Veränderungen des mittleren arteriellen Druckes waren minimal, Anschließend wurde die Auswirkung der endotrachealen Intubation auf den mittleren arteriellen Druck untersucht. In allen Fällen konnte man einen Anstieg des mittleren arteriellen Druckes beobachten. Der Anstieg war bei den Patienten, die Pancuronium erhalten hatten, ausgeprägter und signifikant höher als bei den Patienten mit Org NC45 (P<0,01). Hieraus schließen wir, daß Org NC45 keine hemmende Wirkung auf den Vagus besitzt und daß die unterschiedliche Reaktion auf den Intubationsreiz auf eine Wirkung von Org NC45 und Pancuronium auf den Sympathikus zurückzuführen ist.

COMPARACION DE LOS EFECTOS DEL ORG NC 45 Y DEL BROMURO DE PANCURONIO EN EL RITMO CARDIACO Y EN LA PRESION ARTERIAL DEL HOMBRE ANESTESIADO

SUMARIO
Se estudiaron en el hombre anestesiado los efectos del Org NC 45 y del bromuro de pancuronio sobre el ritmo cardíaco y la presión arterial. Se administró una dosis de 0,12 mg kg⁻¹ de Org NC 45 o de 0,1 mg kg⁻¹ de pancuronio a pacientes sin estimular y ligeramente anestesiados. El ritmo cardíaco disminuyó en la mayoría de los pacientes a raíz del Org NC 45 (media y error típico de 3,78 ± 1,36) mientras que el ritmo cardíaco aumentó después del pancuronio (media y error típico de 11,9 ± 1,9). Los cambios que se observaron en la presión arterial media fueron mínimos. Se estudió seguidamente el efecto de la intubación endotraqueal sobre la presión arterial media. Se observó un incremento de la presión arterial media en todos los pacientes. El incremento fue más notable en aquellos pacientes que habían recibido pancuronio y fue bastante superior al de los pacientes que habían recibido Org NC 45 (P<0,01). Nuestra conclusión es que el Org NC 45 no ejerce bloqueo vagal alguno y que la diferencia de la respuesta ante el estímulo de la intubación endotraqueal es consecuencia de los diferentes efectos que en el sistema nervioso simpático ejercen el Org NC 45 y el pancuronio.