DOSE-RESPONSE RELATION FOR ATRACURIUM, ORG NC45 AND PANCURONIUM

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SUMMARY

The potencies of atracurium, Org NC45 and pancuronium were determined using cumulative dose–response curves. The effective doses producing 95% twitch depression were 279 ng kg\(^{-1}\), 56 \(\mu\)g kg\(^{-1}\) and 64 \(\mu\)g kg\(^{-1}\) respectively, the relative potency being 1:5.0:4.3. The calculated log-probit dose–response curves showed the steepest slope for pancuronium, although the slopes did not deviate significantly from the parallel. The three drugs provided equal and generally good intubating conditions at approximately 95% twitch depression. Greater arterial pressure and heart rate were seen with pancuronium than with atracurium and Org NC45.

Atracurium and Org NC45 are newly developed non-depolarizing neuromuscular blocking drugs which are reported to have intermediate durations of action. Cumulative effects seem to be lacking, and cardiovascular effects are either minimal or absent (Agoston et al., 1980; Cruul and Booij, 1980; Coker et al., 1981; Payne and Hughes, 1981). A comparative study on atracurium and Org NC45 has not been performed and an estimation of their relative potencies is indicated before proceeding with more detailed clinical investigations.

PATIENTS AND METHODS

Thirty female patients, ASA class I, about to undergo gynaecological operations for non-malignant conditions, gave informed consent to the study. Patients were excluded from the study if: pregnant or in the puerperium, receiving medication for infectious or other diseases, body weight deviated by more than 20% from normal (Natvig, 1956), younger than 20 or older than 50 yr of age.

The patients were premedicated 1 h before anaesthesia with pethidine 75 mg and atropine 0.6 mg i.m. Anaesthesia was induced with diazepam 10 mg, fentanyl 0.2 mg and thiopentone 100–500 mg i.v. till the eyelash reflex was abolished, and maintained subsequently during the recordings with 50% nitrous oxide in oxygen using intermittent positive pressure ventilation via a face mask. The patients were randomly allocated to three groups, which received one of the neuromuscular blocking agents: atracurium, Org NC45 or pancuronium. All measurements were made before the start of surgery.

The left ulnar nerve was stimulated electrically at the wrist via subcutaneous needle electrodes connected to a Myotest stimulator (Viby-Mogensen et al., 1980) delivering supramaximal impulses at 0.1 Hz. The force of the adduction of the thumb was measured by a Statham UC3 transducer connected to a Hewlett-Packard 7702B recorder equipped with 8805C amplifier. Resting thumb tension was adjusted to 280 g before the recordings started, and was reassessed after the study to ensure that preload had been maintained between 200 and 300 g.

When the evoked twitch response was stable, the neuromuscular blocking drug was administered in incremental doses to obtain an individual dose–response curve for each patient, using the principles described by Donlon, Ali and Savarese (1974). Each drug was given as five equal increments, the first two increments being injected in one dose to avoid zero-effect. The sizes of the increments were determined from a preceding pilot study on 20 patients who fulfilled the criteria detailed above. The cumulative doses were estimated to give four defined points for each drug on a dose–response curve, the last injection producing about 95% depression of the twitch. The increments were: atracurium 55 \(\mu\)g kg\(^{-1}\), Org NC45 12 \(\mu\)g kg\(^{-1}\) and pancuronium 13 \(\mu\)g kg\(^{-1}\). After the injection of each dose, the twitch response was observed until a maximum effect was obtained, as judged by three consecutive twitches of equal height, before the next incremental dose was given.

When the maximum effect had been achieved after the last incremental dose, the trachea was
intubated. Conditions for intubation were classified according to Lund and Stovner (1970).

At each increment arterial pressure was measured indirectly with a sphygmomanometer and heart rate was registered on an e.c.g. monitor. Mean arterial pressure was assumed to be diastolic pressure plus one-third pulse pressure (Kelman, 1971).

Depression of twitch height was statistically treated in probit values (Finney, 1952), and the presented mean responses are transformed probit means. The composite dose–response curve for each drug was determined by log-probit transformation of the data and calculation by the method of least squares. Other statistical analyses were by Student's t test. Statistical differences were considered significant at $P < 0.05$.

RESULTS

The three groups of patients were of similar age, weight and body surface area (table I).

Mean responses of the four doses of the three drugs are presented in figure 1. Log-probit regression lines are drawn to show the cumulative dose–response relation for each drug. Calculated dose–response values are presented in table II. For 95% blocking doses (ED$_{95}$) the relative potency for atracurium, Org NC45 and pancuronium was 1:5.0:4.3. The difference in potency between Org NC45 and pancuronium was not significant. The slopes of the regression lines were similar and did not deviate significantly from each other.

Conditions for intubation were similar with the three agents at maximum twitch depression (table III). Excellent intubating conditions were obtained when twitch depressions were most marked.

Average arterial pressure and heart rate were greater in the group receiving pancuronium than in the other two groups (fig. 2).

DISCUSSION

Since neuromuscular blockade has a quantal response to drug concentration the pharmacodynamics are suitably described by a log-probit dose–response relationship (Ginsburg, Kitz and Savarese, 1971). Construction of cumulative dose–response curves showed Org NC45 to be about 15% more potent than pancuronium and about five times more potent than atracurium for doses producing 95% depression of twitch response. The dose–response curves were parallel, making these relative potencies valid for other doses also.

**Fig. 1.** Mean cumulative dose–response curves for Org NC45 (N), pancuronium (P) and atracurium (A). Mean twitch depression ± SEM after each incremental dose is indicated.

**Fig. 2.** Mean arterial pressure (MAP) and heart rate (HR) at the four dose–response levels. Mean results ± SEM are expressed as percentage of the control values. The absolute values of the latter are quoted on the figure at 0 dose as mean ± SEM. *$P < 0.05$; **$P < 0.01$.**
DOSE-RESPONSE FOR ATRACURIUM, ORG NC45, PANCURONIUM

The potency of atracurium was previously estimated by Payne and Hughes (1981) who found 81% and 98% depression of twitch height with 200 and 300 μg kg⁻¹ respectively. These results are similar to ours (84.9% and 94.5% after 220 and 275 μg kg⁻¹). The absolute and relative potencies of Org NC 45 and pancuronium in our study were comparable to previous reports (Agoston et al., 1980; Crul and Booij, 1980; Krieg, Hendrickx and Crul, 1981). Fahey and colleagues (1981) found Org NC 45 to be about 1.5 times more potent than pancuronium under halothane anaesthesia. After prior administration of suxamethonium, Krieg, Crul and Booij (1980) found this potency ratio to be about 1.7. The estimated ED₉₅ of pancuronium in our study was similar to their finding (62.2 μg kg⁻¹), but slightly greater than that reported by Donlon and colleagues (1980) (55 μg kg⁻¹, using 0.25 Hz nerve stimulation). The dose–response curve for pancuronium was insignificantly steeper than for Org NC45, which is in agreement with previous reports (Crul and Booij, 1980; Krieg, Crul and Booij, 1980).

The three drugs provided equal and generally good intubating conditions after administration of approximately equipotent doses producing about 95% twitch depression. Donlon, Ali and Savarese (1974) reported on overall adequate intubating conditions at this response level, using 0.25 Hz nerve stimulation. The best conditions for endotracheal intubations were observed in those patients with the most marked depression of twitch response. Statistical comparison between twitch responses at different intubating conditions is omitted because sample sizes are small and unevenly distributed. Krieg and co-workers (1980), using Org NC 45, reported no significant difference in twitch height between patients with different intubating conditions.

Evaluation of cardiovascular effects of the drugs per se cannot be made without a control group. In previous investigations both atracurium and Org NC 45 were reported to be devoid of cardiovascular side-effects (Krieg, Crul and Booij, 1980; Payne and Hughes, 1981). Our study showed little difference between these two drugs, although there was a 6.8% greater decrease in heart rate after Org NC 45 which could, however, be attributed to a 10% higher initial value. Our finding that pancuronium produced a significantly higher arterial pressure than atracurium and significantly more rapid heart rate than both atracurium and Org NC 45, is consistent with previous reports of stable or increased arterial pressure and heart rate after the injection of pan-
curonium (Kelman and Kennedy, 1971; Coleman et al., 1972; Harrison, 1972).

In conclusion, Org NC 45 was found to be five times more potent than atracurium and slightly more potent than pancuronium. The dose–response curves yielded nearly parallel, straight lines on a log-probit diagram. The relative potencies at ED$_{50}$ are therefore likely to be valid also for the larger doses commonly used in anaesthesia. Equally good intubating conditions at 95% twitch depression indicate that the clinical dose range for the drugs will correspond to their estimated potency ratio. The lack of chronotropic and hypertensive effects of atracurium and Org NC 45 may make the drugs acceptable in relatively greater doses than pancuronium.

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REFERENCES


RELATION DOSE–RESPONSE DE L'ATRACURIUM, DE L’ORG NC45 ET DU PANCURONIUM

Résumé

Nous avons déterminé les puissances de l’atracurium, de l’Org NC 45 et du pancuronium en utilisant les courbes dose–réponse cumulatives. Les doses efficaces entraînant une dépression de 95% du twitch étaient 279 µg kg$^{-1}$, 356 µg kg$^{-1}$ et 69 µg kg$^{-1}$ respectivement, la puissance relative étant 1:5:0:4,3. Les courbes dose–réponse calculées "log-probit" ont fait apparaître la pente la plus raide pour le pancuronium, bien que les pentes ne s'écartent pas significativement de parallèles. Les trois agents ont fourni des conditions d'intubation équivalentes et bonnes dans l'ensemble à environ 95% de dépression du twitch. La pression artérielle et la fréquence cardiaque étaient plus élevées avec le pancuronium qu'avec l'atracurium et l'Org NC 45.

DOSSER–WIRKUNGSBEZIEHUNG FÜR ATRACURIUM, ORG NC 45 UND PANCURONIUM

ZUSAMMENFASSUNG

RELACION DE DOSIS-RESPUESTA PARA EL ATRACURIO, EL ORG NC45 Y EL PANCURONIO

SUMARIO
Se determinaron las potencias del atracurio, del Org NC 45 y del pancuronio haciendo uso de curvas acumulativas de dosis-respuesta. Las dosis efectivas que produjeron una depresión espasmódica del 95% fueron de 279 μg·kg⁻¹, 56 μg·kg⁻¹ y 64 μg·kg⁻¹ respectivamente; siendo la potencia relativa de 1:5,0:4,3. Las curvas logarítmicas de dosis-respuesta mostraron las mayores pendientes para el pancuronio, aunque todas ellas fueron paralelas sin cambios significativos. Las tres drogas presentaron condiciones de intubación iguales y generalmente buenas a una depresión espasmódica de aproximadamente el 95%. Se apreció un mayor ritmo cardíaco y presión arterial con el pancuronio que con el atracurio y el Org NC45.