Br. J. Anaesth. (1981), 53, 627

DOSE–RESPONSE CURVES FOR FOUR NEUROMUSCULAR BLOCKERS USING CONTINUOUS I.V. INFUSION

C. A. SHANKS, J. S. WALKER, M. I. RAMZAN AND E. J. TRIGGS

SUMMARY

Cumulative dose–response curves were constructed in man for tubocurarine, pancuronium, gallamine and alcuronium from data obtained during barbiturate–narcotic–nitrous oxide anaesthesia. Fifty-six adult patients received one of these drugs, administered by constant-rate infusion, a technique enabling full characterization of the sigmoid curve for each patient. The individual curves were solved for several response levels and the results pooled to derive a composite dose–response curve for each drug. Using the mechanical twitch response, the ED_{50} for each neuromuscular blocking drug was: tubocurarine 0.236 mg kg^{-1}, pancuronium 0.048 mg kg^{-1}, gallamine 1.3 mg kg^{-1} and alcuronium 0.161 mg kg^{-1}. The slopes of the composite curves for pancuronium and alcuronium were significantly steeper than those for tubocurarine and gallamine. In the alcuronium studies the simultaneous compound electromyogram was recorded, and usually this was more depressed than the mechanical twitch response, giving an ED_{50} of 0.135 mg kg^{-1}.

Many studies have examined the dose–response relationships of the non-depolarizing neuromuscular blocking drugs during anaesthesia, most authors assessing the response in terms of the evoked single twitch response. However, many factors affect the dose–reponse curve, including the method by which the twitch is evoked. Rigorous techniques of motor nerve stimulation require a wave-form of short duration and correct polarity delivered at a truly supramaximal voltage. Further, for single events, the frequency of stimulation must allow sufficient time for each twitch response to recover from the effects of its predecessor. Slower stimulus frequencies produce dose–response curves which are to the right of those with more rapid rates (Savarese, Ali and Antonio, 1977; Shanks, Ramzan and Triggs, 1979; Ali and Savarese, 1980). The evoked muscular responses can be measured as the mechanical tension or the compound muscle action potential (e.m.g). While most authors have used the mechanical twitch tension in investigating dose–response relationships, it is likely that electromyographic techniques will become more widely used, as they avoid problems with transducer fixation, orientation overload and preload (Gissen, 1973; Donlon, Savarese and Ali, 1979).

Cumulative dose–response curves based on incremental i.v. doses of neuromuscular blocker seldom use more than five doses, but more data points are available when the agent is administered by constant-rate infusion. The present studies use such an infusion technique to compare the relative potencies of four non-depolarizing agents: alcuronium, gallamine, pancuronium and tubocurarine. The alcuronium study was extended by simultaneous measurement of the mechanical and electrical responses.

PATIENTS AND MATERIALS

Dose–response curves were obtained from studies on 56 adult patients during the 1st hour of elective surgery (herniorraphy or peripheral vascular procedure). Informed consent was obtained from each patient.

Following premedication, anaesthesia was induced with droperidol 5–10 mg, phenoperidine 0.5 mg and thiopentone 100–300 mg i.v. Topical application of lignocaine to the larynx facilitated placement of an endotracheal tube. Further increments of phenoperidine or thiopentone were added as necessary to maintain the barbiturate–nitrous oxide–narcotic anaesthesia. Ventilation with 70% nitrous oxide in oxygen was adjusted to maintain an end-expired carbon dioxide concentration of 5%. Deep body and limb hypothermia were avoided.

C. A. SHANKS, M.D., F.F.A.R.C.S., Department of Anaesthetics, Royal Prince Alfred Hospital, Camperdown, Sydney, Australia. J. S. WALKER, DIP.PHARM.; M. I. RAMZAN, M.SC.; E. J. TRIGGS,* PH.D.; Department of Pharmacy, University of Sydney, Sydney, Australia.

* Present address: University of Queensland (Department of Pharmacy), St Lucia, Queensland, 4067, Australia.

0007–0912/81/060627–07 $01.00

The ulnar nerve was stimulated supramaximally at the elbow every 10 s (0.1 Hz), using impulses of 0.1–0.15 s duration, at a nominal voltage output of up to 500 V delivered via surface electrodes. The mechanical twitch response was recorded from an immobilized upper limb, using a linear force transducer applied at right angles to the thumb with a preload of some 200 g. The compound muscle action potentials (e.m.g.) were obtained from the small muscles of the first interspace of the same hand via surface electrodes placed dorsally. The e.m.g. response was processed by a modified Neurolog 750 signal averaging system (Digitimer, Herts). This reconverted the gated signal from digital to analog during the interval between stimuli, so that simultaneous e.m.g. and mechanical responses were recorded on the chart recorder. The intensity of paralysis was assessed from the depression of the mechanical twitch response or e.m.g. amplitude from its control height.

The 56 patients were divided into four groups according to the drug used. A constant-rate infusion was administered of alcuronium $10\,\mu g\,kg^{-1}\,min^{-1}$, gallamine $80\,\mu g\,kg^{-1}\,min^{-1}$, pancuronium $4\,\mu g\,kg^{-1}\,min^{-1}$ or tubocurarine $9.3\,\mu g\,kg^{-1}\,min^{-1}$. Using the mechanical twitch response, dose–response curves were constructed for each patient. These curves were solved to determine the effective doses for 30, 50, 80 and 95% twitch suppression.

The dose–response curves were fitted to the Hill equation in the form:

$$\text{Response} = \frac{100\% \,.\, D^s}{K^s + D^s}$$

where the response (percent paralysis) is described as a fraction of its maximum (100%) in terms of the variable dose (D) the mean effective dose at 50% paralysis (K, a constant) and a power function (s). The data were fitted to the equation by an iterative least-squared non-linear regression analysis, with K and s as the unknown values. From the fitted curves for each patient were derived the dosage for 5%, each decile and the 95% responses, and the means of these 11 response values were used to produce a composite curve for 5–95% paralysis. In the range between 20 and 80% the linear portion of the log dose–response composite curves were tested for parallelism.

Further studies of dose–response relationships were performed in the group to whom alcuronium was administered. Cumulative dosage was calculated additionally as its absolute total and as μg

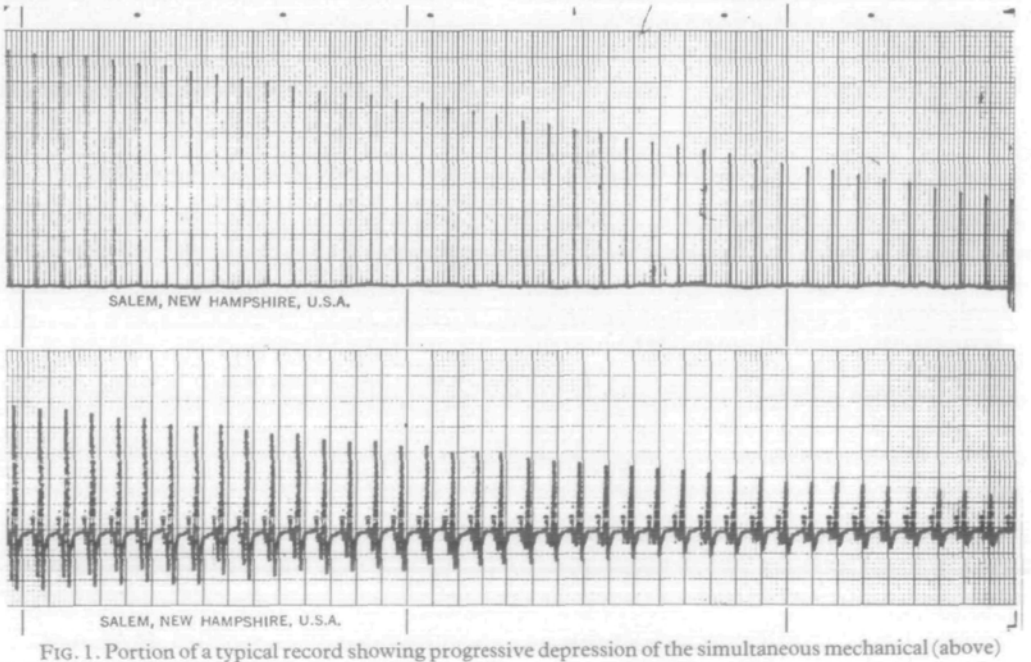

FIG. 1. Portion of a typical record showing progressive depression of the simultaneous mechanical (above) and electrical responses during the infusion. The e.m.g. amplitude is depressed more than is the concurrent mechanical twitch height.

per m^2 of body surface area. These doses were then related to the simultaneous mechanical and e.m.g. responses.

RESULTS

A portion of a typical recording is shown in figure 1. Following the start of the infusion of neuromuscular blocker, several minutes elapsed before any changes could be seen. Not infrequently there was an initial increase in the height of the evoked mechanical twitch response. This was usually at or above its control height when the e.m.g. amplitude began to decrease. Thereafter, the two decreased roughly in parallel. Pooled data at four response levels in each group are shown in table I. The values for best fit of the composite data to the Hill equation are shown in table II and figure 2. The slopes of the (log) dose–response curves in their control range are slightly more than half the values given for the power functions. The composite curves for tubocurarine and gallamine appear to be parallel, but those for both pancuronium and alcuronium are steeper ($P < 0.01$).

The individual solutions which give the best fit of ED_{50} and to the Hill equation dose–response curves for alcuronium are shown in table III, with the values for the composite curves. When these were pooled to derive table I values for alcuronium and for its other five composite curves, the variances indicated an advantage in examining the dose in terms of body weight. The correlation coefficients for the non-linear regression analysis

TABLE I. *Cumulative dosage (mg kg^{-1}, mean ± SD) at four response levels, derived from the individually fitted curves for each patient*

	Percent paralysis			
	30%	50%	80%	95%
Alcuronium	0.136 (0.038)	0.161 (0.042)	0.210 (0.052)	0.286 (0.068)
Gallamine	1.050 (0.383)	1.295 (0.401)	1.850 (0.454)	2.820 (0.790)
Pancuronium	0.042 (0.009)	0.048 (0.010)	0.061 (0.012)	0.080 (0.018)
Tubocurarine	0.184 (0.054)	0.235 (0.068)	0.353 (0.108)	0.561 (0.109)

TABLE II. *Values for best fit of data to the Hill equation*

	ED_{50} (mg kg^{-1})	s
Alcuronium	0.161	5.16
Gallamine	1.300	3.86
Pancuronium	0.048	5.84
Tubocurarine	0.236	3.41

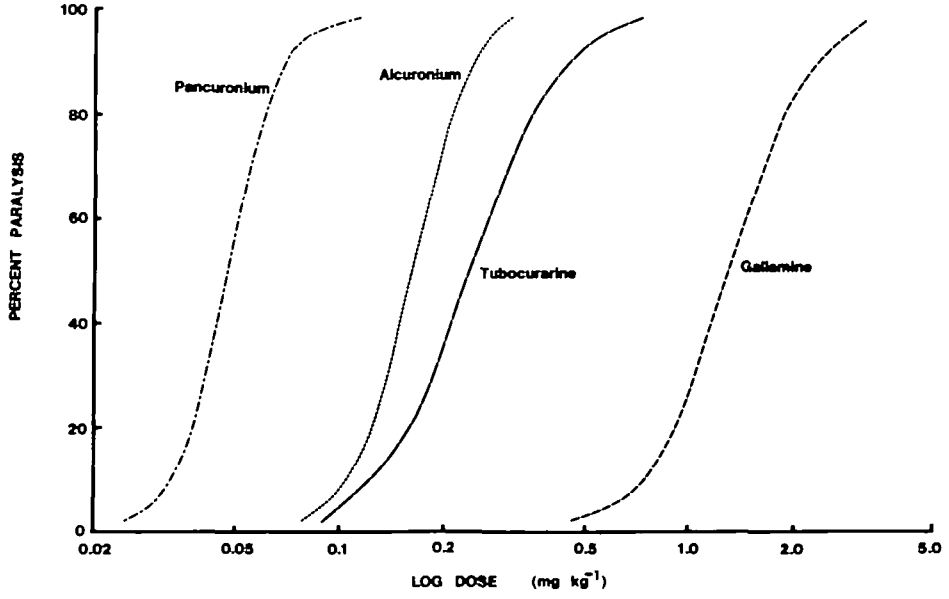

FIG. 2. The composite dose–response curves for pancuronium, alcuronium, tubocurarine and gallamine (from left to right). The steeper slopes of the two former curves reflect their greater values for the power function in table II.

in table III exceeds 0.99 in all but one subject, where the e.m.g. results gave it as greater than 0.987.

TABLE III. *Individual dose–response curves for alcuronium*

Patient no.	Dose			s
	$mg\,kg^{-1}$	$mg\,m^{-2}$	mg total	
(A) Assessed by the mechanical twitch response				
1	0.143	5.418	10.987	4.04
2	0.122	5.277	10.749	4.18
3	0.201	8.550	15.668	7.60
4	0.235	9.440	19.022	4.84
5	0.115	4.878	8.533	5.30
6	0.130	4.401	6.777	6.07
7	0.136	5.454	9.818	4.57
8	0.133	4.898	7.835	5.41
9	0.147	5.160	8.646	4.73
10	0.163	5.828	10.567	5.16
11	0.163	6.163	11.110	4.81
12	0.154	6.027	11.246	4.40
13	0.149	5.873	10.246	6.02
14	0.257	9.625	16.988	5.99
Mean	0.161	6.214	11.299	
SD	(0.042)	(1.705)	3.536	
Composite				
ED_{50}	0.161	6.217	11.304	
s	5.16	5.15	5.12	
(B) Assessed by the e.m.g. response				
1	0.106	4.022	8.154	4.26
2	0.128	5.522	11.249	4.40
3	0.177	7.439	13.794	6.54
4	0.160	6.425	12.947	4.92
5	0.095	4.031	7.051	4.75
6	0.118	3.984	6.136	4.71
7	0.122	4.882	8.787	4.98
8	0.111	4.086	5.637	4.98
9	0.126	4.436	7.433	5.13
10	0.141	4.036	9.131	4.66
11	0.144	5.443	9.796	4.27
12	0.128	4.997	9.323	4.88
13	0.133	5.258	9.173	7.03
14	0.206	7.693	13.579	4.85
Mean	0.135	5.232	9.442	
SD	(0.029)	(1.212)	(2.619)	
Composite				
ED_{50}	0.135	5.234	9.445	
s	4.97	4.98	4.97	

DISCUSSION

The administration of a non-depolarizing neuromuscular blocking drug by constant-rate infusion has advantages in that the cumulative dosage can be calculated from the time-base of the response record and that it provides many points for the construction of dose–response curves. Previously, we studied the curves for pancuronium using infusions which were more rapid or slower than $4\,\mu g\,kg^{-1}\,min^{-1}$ (Shanks, Somogyi and Triggs, 1979). Rapid infusion underestimates the response, as it does not allow time for the maximum development of paralysis; slow infusion will overestimate dosage as this permits distribution of the drug to poorly perfused tissues and the commencement of excretion. Elucidating this, Sheiner and his colleagues (1979) have developed a pharmacodynamic model that uses a first-order rate constant to characterize the "temporal disequilibrium" and which uses the Hill equation to characterize sensitivity.

If single stimuli are applied at rates which are sufficiently slow (0.15–0.1 Hz), the dose–response curves for neuromuscular blockers in man are not shifted to the left (Savarese, Ali and Antonio, 1977). These authors gave ED_{95} values for pancuronium and tubocurarine of 0.07 and $0.51\,mg\,kg^{-1}$ respectively. ED_{50} values in studies using slow rates of stimulation have given results for tubocurarine of 0.26 and $0.25\,mg\,kg^{-1}$ (Savarese, Ali and Antonio, 1977; Ali and Savarese, 1980) and for pancuronium of 0.036, 0.041 and $0.056\,mg\,kg^{-1}$ (Savarese, Ali and Antonio, 1977, Miller et al., 1978; Shanks, Somogyi and Triggs, 1979). More rapid rates of stimulation shift the dose–response curve for tubocurarine to the left (Ali and Savarese, 1980; Shanks, Ramzan and Triggs, 1979). The values in table I are approximately 60% greater than the results reported by Donlon, Ali and Savarese (1974), who used a stimulation rate of 0.25 Hz. As more rapid stimulation and the presence of potent inhalation agents both affect the dose–response relationships, it is not surprising that this combination often reduces the values for ED_{50} in table II by a half or more (Miller, 1973; Goudsouzian et al., 1975). These authors also agreed that the curves of tubocurarine and gallamine are parallel. Lund and Stovner (1970) reported previously that the slopes of the dose–response curves for alcuronium and for pancuronium were steeper than that for tubocurarine. Donlon, Ali and Savarese (1974) reported that the slope for pancuronium was significantly steeper than those for gallamine, tubocurarine and metocurine.

Table III indicates that the alcuronium dose–response curves, as measured by the mechanical and electrical responses, had much the same slopes. However, the e.m.g. values gave curves to

the left of those obtained from the mechanical twitch response. This was unexpected as studies with the administration of tubocurarine had shown that the block recorded mechanically was usually greater than that recorded electrically (Epstein and Epstein, 1973; Katz, 1973). Differences with these studies and ours include a stimulation rate of 0.2 Hz and the use of tetanic trains.

In practical terms the steepness of the slope could determine drug usuage clinically. The dose which produces a minimal block, 5% paralysis, is related by the composite curves (table II) to the ED_{95}. For pancuronium and alcuronium a total of approximately triple this initial amount would be predicted, whereas gallamine and tubocurarine would require about five times as much to produce 95% paralysis.

The slopes of the curves in table II are in reasonable agreement with other studies involving gallamine, pancuronium and tubocurarine. In the absence of studies giving comparable dose–response curves for alcuronium it is likely that it would resemble tubocurarine in that the ED_{95} value at 0.1 Hz would be the dose providing satisfactory conditions for endotracheal intubation (Ali and Savarese, 1980). Most authors report (Lund and Stovner, 1962; Bush, 1965; Baraka, 1967; Dwyer, Gunner and Walker, 1967) that, clinically, alcuronium is approximately twice as potent as tubocurarine. This is in good agreement with the ratio for these two drugs based on their ED_{95} in table I. Miller and Eger (1976) reported a difference between the early and late relative potencies of pancuronium and tubocurarine. Their early relative potency ratio of 7.4 is in agreement with the ED_{95} ratio derived from table I. For the early relative potency, it is possible to calculate the ED_{95} bolus dose of a neuromuscular blocker by multiplication of the volume of distribution (area) and the plasma concentration associated with 95% paralysis obtained during offset of its action, table IV shows the bolus doses for tubocurarine and pancuronium as calculated previously (Shanks et al., 1980), and for means of pooled data from studies involving gallamine and alcuronium (Ramzan, Triggs and Shanks, 1980; Walker, Triggs and Shanks, 1980).

The relationship between dose and response may be examined in terms of the intensity of effect, as above, or in terms of the duration of useful effect. The latter is well assessed by means of a steady-state response, the infusion dosage being used to calculate the late relative potencies. Mitenko and Ogilvie (1972) suggested a bolus and infusion regime to achieve a steady-state plasma concentration, the infusion rate being calculated from the product of the desired concentration and the plasma clearance rate. Our data would suggest alcuronium $1.2\,\mu g\,kg^{-1}\,min^{-1}$, gallamine $13.1\,\mu g\,kg^{-1}\,min^{-1}$, pancuronium $0.49\,\mu g\,kg^{-1}\,min^{-1}$ and tubocurarine $2.8\,\mu g\,kg^{-1}\,min^{-1}$ should be combined with the doses in table IV.

TABLE IV. *Calculation of the ED_{95} bolus dose of a neuromuscular blocker.* * *Associated with 95% block during recovery from paralysis (stimulus frequency, 0.1 Hz).* † *From Ramzan, Triggs and Shanks (1980);* ‡ *from Walker, Triggs and Shanks (1980)*

	Volume of distribution (litre kg^{-1})	Plasma concentration (mg $litre^{-1}$)*	Calculated ED_{95} (mg kg^{-1})
Alcuronium‡	0.373	0.74	0.28
Gallamine†	0.270	9.96	2.69
Pancuronium	0.307	0.25	0.08
Tubocurarine	0.609	0.96	0.58

ACKNOWLEDGEMENTS

These studies were supported by the Australian National Health and Medical Research Council and by Organon (Australia).

REFERENCES

Ali, H. H., and Savarese, J. J. (1980). Stimulus frequency and dose–response curve to tubocurarine in man. *Anesthiology*, **52**, 36.

Baraka, A. (1967). A comparative study between diallylnortoxiferine and tubocurarine. *Br. J. Anaesth.*, **39**, 624.

Bush, G. H. (1965). The clinical comparison between tubocurarine and diallylnortoxiferine in children. *Br. J. Anaesth.*, **37**, 540.

Donlon, J. V., Ali, H. H., and Savarese, J. J. (1974). A new approach to the study of four non-depolarizing relaxants in man. *Anesth. Analg. (Cleve.)*, **53**, 934.

—— Savarese, J. J., and Ali, H. H. (1979). Cumulative dose–response curves for gallamine: effect of altered resting thumb tension and mode of stimulation. *Anesth. Analg. (Cleve.)*, **58**, 377.

Dwyer, B. E., Gunner, B. W., and Walker, W. D. (1967). Diallyl-nortoxiferine ("Alloferin"). A clinical appraisal. *Austr. N. Z. J. Surg.*, **37**, 54.

Epstein, R. A., and Epstein, R. M. (1973). The electromyogram and the mechanical response of indirectly stimulated muscle in anesthetized man following curarization. *Anesthesiology*, **38**, 212.

Gissen, A. J. (1973). Standardized technique for transmission studies. *Anesthesiology*, **39**, 567.

Goudsouzian, N. G., Donlon, J. V., Savarese, J. J., and Ryan, J. F. (1975). Re-evaluation of dosage and duration of action of d-tubocurarine in the pediatric age group. *Anesthesiology*, **43**, 416.

Katz, R. L. (1973). Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch tetanic and post-tetanic response. *Br. J. Anaesth.*, **45**, 849.

Lund, I., and Stovner, J. (1962). Potency and reversibility by prostigmine of RO 4-3816 and d-tubocurarine. *Acta Anaesthesiol. Scand.*, **6**, 161.

—— —— (1970). Dose–response curves for tubocurarine, alcuronium and pancuronium. *Acta Anaesthesiol. Scand.*, (Suppl.), **37**, 238.

Miller, R. D. (1973). Neostigmine antagonism of neuromuscular block. *Anesthesiology*, **38**, 511.

—— Agoston, S., Booij, L. H. D. J., Kersten, U. W., Crul, J. F., and Ham, J. (1978). The comparative potency and pharmacokinetics of pancuronium and its metabolites in anaesthetized man. *J. Pharmacol. Exp. Ther.*, **207**, 539.

—— Eger, E. I. (1976). Early and late relative potencies of pancuronium and d-tubocurarine in man. *Anesthesiology*, **44**, 297.

Mitenko, P. A., and Ogilvie, R. I. (1972). Rapidly achieved plasma concentration plateaux, with observations on theophylline kinetics. *Clin. Pharmacol. Ther.*, **13**, 329.

Ramzan, M. I., Triggs, E. J., and Shanks, C. A. (1980). Pharmacokinetic studies in man with gallamine triethiodide. *Eur. J. Clin. Pharmacol.*, **17**, 135.

Savarese, J. J., Ali, H. H., and Antonio, R. P. (1977). The clinical pharmacology of metocurine: dimethyltubocurarine revisitied. *Anesthesiology*, **47**, 277.

Shanks, C. A., Ramzan, M. I., and Triggs, E. J. (1979). Studies in man with constant-rate i.v. infusion of tubocurarine. Tubocurarine and pancuronium: a pharmacokinetic view. *Anaesth. Intens. Care*, **7**, 209.

—— Somogyi, A. A., Ramzan, M. I., and Triggs, E. J. (1980). *Anaesth. Intens. Care*, **8**, 4.

—— —— Triggs, E. J. (1979). Dose–response and plasma concentration response relationships of pancuronium in man. *Anesthesiology*, **51**, 111.

Sheiner, L. B., Stanski, D. R., Vozeh, S., Miller, R. D., and Ham, J. (1979). Simultaneous modelling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin. Pharmacol. Ther.*, **25**, 358.

Walker, J. S., Triggs, E. J., and Shanks, C. A. (1980). Clinical pharmacokinetics of alcuronium chloride in man. *Eur. J. Clin. Pharmacol.*, **17**, 449.

COURBES DOSES–REACTION DE QUATRE AGENTS DE BLOCAGE NEUROMUSCULAIRE ADMINISTRES PAR PERFUSION INTRAVEINEUSE CONTINUE

RESUME

On a tracé les courbes cumulatives doses–réaction chez l'homme de la tubocurarine, du pancuronium, de la gallamine et de l'alcuronium à partir de données obtenues pendant une anesthésie provoquée par des barbituriques–narcotiques et par le protoxyde d'azote. Cinquante-six patients adultes ont reçu l'un de ces agents, administré par perfusion à taux constant, cette technique permettant d'obtenir la caractérisation complète de la courbe sigmoïde pour chaque patient. On a résolu chacune des courbes pour plusieurs niveaux de réaction et les résultats ont été regroupés pour obtenir une courbe composée dose–réaction pour chaque agent. A l'aide de la réaction à la crispation mécanique, l'ED_{50} pour chaque agent de blocage neuromusculaire a été: tubocurarine 0,236 mg kg^{-1}, pancuronium 0,048 mg kg^{-1}, gallamine 1,3 mg kg^{-1} et alcuronium 0,161 mg kg^{-1}. L'inclinaison des courbes composées pour le pancuronium et l'alcuronium ont été nettement plus prononcées que celles se rapportant à la tubocurarine et à la gallamine. Dans les études faites sur l'alcuronium, on a enregistré l'électromyogramme composé simultané et dans l'ensemble celui-ci a été plus déprimé que la réaction à la crispation mécanique, donnant un ED_{50} de 0,135 mg kg^{-1}.

DOSISREAKTIONSKURVEN FÜR VIER NEUROMUSKULÄRE BLOCKIERUNGSMITTEL BEI KONTINUIERLICHER INTRAVENÖSER INFUSION

ZUSAMMENFASSUNG

Kumulative Dosisreaktionskurven bei Menschen wurden für Tubocurarin, Pancuronium, Gallamin und Alcuronium aus Daten konstruiert, die während einer Barbiturat-Narkotik-Stickoxydnarkose gewonnen wurden. Sechs und fünfzig wachsene Patienten erhielten eine dieser Drogen durch kontinuierliche Infusion—eine Methode, die die genaue Charakterisierung der S-förmigen Kurve für jeden Patienten ermöglicht. Die einzelnen Kurven wurden nach mehreren Reaktionsstufen untersucht, und die gemeinsamen Resultate zur Erstellung einer zusammengesetzten Dosisreaktionskurve für jede der Drogen benutzt. Unter Verwendung der mechanischen Zukkungsreaktion betrug ED_{50} für die einzelnen neuromuskulären Blockierungsdrogen: Tubocurarin 0,236 mg kg^{-1}, Pancuronium 0,048 mg kg^{-1}, Gallamin 1,3 mg kg^{-1} und Alcuronium 0,161 mg kg^{-1}. Das Gefälle der zusammengesetzten Kurven für Pancuronium und Alcuronium war wesentlich steiler als das für Tubocurarin und Gallamin. Bei den Alcuronium-Studien wurde auch das gleichzeitig ermittelte Elektromyogramm aufgezeichnet, und es war meist mehr unterdrückt als die mechanische Zukkungsreaktion—ED_{50} von 0,135 mg kg^{-1}.

CURVAS DE DOSIS-RESPUESTA CORRESPONDIENTES A CUATRO AGENTES DE BLOQUEO NEUROMUSCULAR AL USAR INFUSION INTRAVENOSA CONTINUA

SUMARIO

Se construyeron curvas acumulativas de dosis–respuesta para el hombre, correspondientes a la tubocuranina, al pancuronio, a la gallamina y al alcuronio, apartir de la información obtenida durante la anestesia con barbitúricos-narcoticos-óxido nitroso.

Cincuenta y seis pacientes adultos recibieron una de estas drogas, administradas mediante infusión a ritmo constante, que es una técnica que hace posible la total caracterización de la curva sigmoide para cada paciente. Se efectuaron las curvas individuales para diferentes niveles de respuesta y los resultados se amalgamaron para poder derivar una curva de dosis–respuesta compuesta para cada una de las drogas. Haciendo uso de la respuesta de sacudida mecánica, la ED_{50} para cada uno de los agentes de bloqueo neuromuscular fue: 0,236 mg kg^{-1} de tubocuaranina; 0,048 mg kg^{-1} de pancuronio; 1,3 mg kg^{-1} de gallamina y 0,161 mg kg^{-1} de alcuronio. Las pendientes de las curvas compuestas para el alcuronio y el pancuronio fueron significativamente más empinadas que las correspondientes a la tubocuranina y a la gallamina. En los estudios del alcuronio se registró el electromiograma compuesto y simultáneo, siendo normalmente éste más deprimido que la respuesta de la sacudida mecánica, produciendo una ED_{50} de 0,135 mg kg^{-1}.