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PHARMACOKINETICS OF ATRACURIUM BESYLATE IN HEALTHY PATIENTS (AFTER A SINGLE I.V. BOLUS DOSE)

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SUMMARY

The plasma decay of atracurium besylate was examined in two groups of six patients. Group I received atracurium 0.6 mg kg^{-1} and group II 0.3 mg kg^{-1} as a single bolus dose i.v. The plasma concentrations were measured by high performance liquid chromatography. An individual two-compartment pharmacokinetic model was used for interpretation. The results from the two groups were not significantly different, giving overall mean values of 2 min (±0.2 SEM) for the distribution half-life ($T_{\frac{1}{2}}^{\alpha}$), 19.9 min (±0.6) for the elimination half-life ($T_{\frac{1}{2}}^{\beta}$), 5.5 ml min^{-1} kg^{-1} (±0.2) for total clearance (Cl) and 157 ml kg^{-1} (±7) for total distribution volume (V_{area}).

Atracurium besylate, a new non-depolarizing neuromuscular blocking agent, has been studied in laboratory animals (Hughes and Chapple, 1980; 1981) and anaesthetized man (Payne and Hughes, 1981). In man, it was found that its duration of action was remarkably predictable and was dose-dependent. In addition, a lack of cumulation with repeated doses was demonstrated. *In vitro*, in human plasma, the half-life of the drug was similar to that in buffer at the same pH being approximately 25 min (Hughes and Chapple, 1980). *In vivo*, in cats, the elimination of the drug was observed to be independent of renal and hepatic function, being mainly effected by non-enzymatic pH-dependent decomposition by "Hofmann Elimination" (Hughes and Chapple, 1981).

To determine the plasma half-life and other pharmacokinetic parameters of atracurium in man, two bolus doses (0.6 mg kg^{-1} and 0.3 mg kg^{-1}) were administered i.v. to healthy patients undergoing minor surgery.

PATIENTS AND METHODS

Patients

Twelve patients (ASA 1) undergoing routine minor surgery were included in the study. Each was examined clinically before operation and written consent obtained. The patients (seven male), were aged between 24 and 69 yr and had an average weight of 75 kg. They were divided into two groups: group I received atracurium 0.6 mg kg^{-1} and group II 0.3 mg kg^{-1}. A standard anaesthetic technique was used. Each patient was premedicated with lorazepam 2–3 mg and metoclopramide 10 mg by mouth. Anaesthesia was induced with thiopentone 200–500 mg and maintained with 66% nitrous oxide in oxygen and 0.5–1.0% halothane. Ventilation was controlled throughout the surgical procedure and neuromuscular blockade reversed if necessary with atropine 1.2 mg and neostigmine 2.5 mg. Tracheal intubation was facilitated with halothane (four patients) or atracurium (eight patients). Physiological tensions of carbon dioxide were maintained throughout the study.

The predetermined dose of atracurium was injected i.v. in the back of the left hand and the cannula flushed with physiological saline. Venous blood samples were taken from a catheter in the right antecubital vein at 0, 1.5, 3, 6, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min. Plasma was separated within 30 s by an Eppendorf 5414 bench centrifuge, immediately transferred to glass vials and embedded in "cardice" to freeze it.

Analytical technique

The plasma concentrations of unchanged atracurium were measured by high performance liquid chromatography (HPLC) (Neill and Jones, 1982). Standard concentrations of atracurium in plasma were prepared in triplicate on the day of study for calibration. Each sample was measured in duplicate within 24 h and mean values recorded.

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The assay was accurate to 0.05 $\mu g\,ml^{-1}$.

Calculations

Each set of data was examined as a semi-log plot and fitted to a two-component exponential by the method of non-linear least squares analysis. From the two component exponential:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

(Gibaldi and Perrier, 1975; Greenblatt and Koch-Weser, 1975)—the distribution half-life $T_{\frac{1}{2}}^{\alpha}$, the elimination half-life $T_{\frac{1}{2}}^{\beta}$ and the volume of the central compartment (V_1) were calculated. The total clearance (Cl) and apparent total distribution volume (V_{area}) were calculated from the "area under the curve" (AUC) where:

$$\text{AUC} = \frac{A}{\alpha} + \frac{B}{\beta}$$

$$\text{Clearance } (Cl) = \frac{Xd}{\text{AUC}} \quad (Xd = \text{Dose})$$

$$V_{area} = \frac{Xd}{\text{AUC}.\beta}$$

Pharmacokinetic symbols are those described by Hull (1979).

RESULTS

The plasma decay curves for atracurium from patient 3 in group I and patient 4 in group II have been plotted (fig. 1). The full pharmacokinetic data were calculated and appear in tables I (group I) and II (group II). The Student's *t* test revealed no significant differences between any of the indices in group I when compared with those in group II (table III). The mean values, of the combined results (± SEM), were 19.9 (±0.6) min for the elimination half-life,

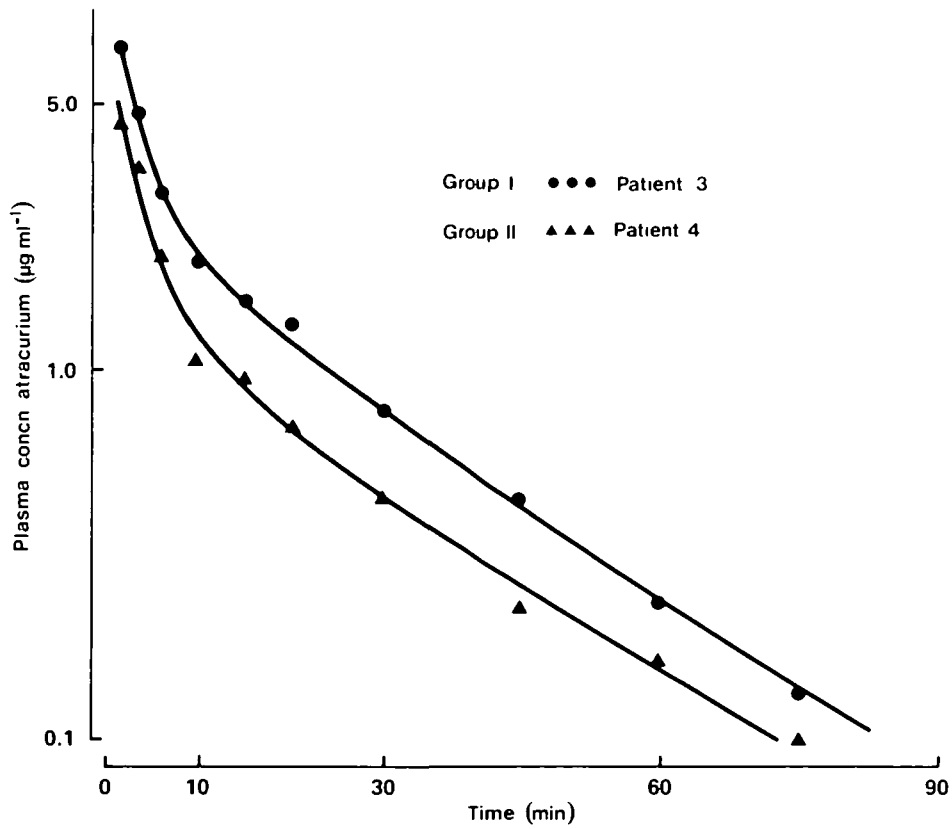

FIG. 1. Semi-log of plasma decay of atracurium after i.v. bolus dose to one patient in group I (0.52 mg kg^{-1}) and one patient in group II (0.32 mg kg^{-1}).

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TABLE I. *Pharmacokinetic values for group I (atracurium 0.6 mg kg^{-1})*

	Patient no.					
	1	2	3	4	5	6
Weight (kg)	65	66	58	89	80	63
Dose (mg)	36	36	30	60	50	40
(mg kg^{-1})	0.55	0.55	0.52	0.68	0.63	0.63
A (μg ml^{-1})	9.7	10.3	8.4	17.0	21.9	6.5
B (μg ml^{-1})	2.3	2.6	2.8	2.8	2.9	2.7
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.8	1.6	1.7	1.3	1.4	2.3
$T_{\frac{1}{2}}^{\beta}$ (min)	21.7	23.1	16.9	21.7	20.4	19.8
Cl (ml min^{-1} kg^{-1})	5.0	4.9	6.0	5.7	4.8	6.5
V_1 (ml kg^{-1})	46	42	47	34	25	69
V_{area} (ml kg^{-1})	157	164	145	178	142	186

TABLE II. *Pharmacokinetic values for group II (atracurium 0.3 mg kg^{-1})*

	Patient no.					
	1	2	3	4	5	6
Weight (kg)	80	97	91	79	69	66
Dose (mg)	25	30	30	25	20	20
(mg kg^{-1})	0.31	0.31	0.33	0.32	0.29	0.30
A (μg ml^{-1})	2.5	5.2	9.9	5.0	3.4	2.8
B (μg ml^{-1})	1.5	2.0	1.8	1.2	2.0	1.2
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.2	2.0	1.0	2.7	2.4	3.3
$T_{\frac{1}{2}}^{\beta}$ (min)	19.8	19.0	17.8	22.4	16.1	20.6
Cl (ml min^{-1} kg^{-1})	6.2	4.4	5.5	5.5	4.9	6.4
V_1 (ml kg^{-1})	78	43	28	51	53	76
V_{area} (ml kg^{-1})	176	120	140	178	114	188

TABLE III. *Comparison of pharmacokinetic values between patients receiving atracurium 0.6 mg kg^{-1} (group I) and 0.3 mg kg^{-1} (group II). The test revealed no significant differences between groups I and II*

	Group I (Mean ± SEM) (n = 6)	Group II (Mean ± SEM) (n = 6)	Group I + II (Mean ± SEM) (n = 12)
Dose (mg kg^{-1})	0.59	0.31	
$T_{\frac{1}{2}}^{\alpha}$ (min)	1.85 ± 0.24	2.27 ± 0.32	2.06 ± 0.20
$T_{\frac{1}{2}}^{\beta}$ (min)	20.6 ± 0.9	19.3 ± 0.9	19.9 ± 0.6
Cl (ml min^{-1} kg^{-1})	5.5 ± 0.3	5.5 ± 0.3	5.5 ± 0.2
V_1 (ml kg^{-1})	44 ± 6	55 ± 8	49 ± 5
V (ml kg^{-1})	162 ± 13	153 ± 13	157 ± 7

5.5 (± 0.2) ml min^{-1} kg^{-1} total clearance and 157 (± 7) ml kg^{-1} total distribution volume (V_{area}).

DISCUSSION

Previous pharmacodynamic studies have shown that the duration of action of atracurium was more predictable than that of any other non-depolarizing neuromuscular blocking drug in common use (Payne and Hughes, 1981). The present study has determined the pharmacokinetics of atracurium following a single bolus dose i.v. and demonstrated an elimination half-life of 19.9 min: a value significantly less than that determined for pancuronium (approximately 100 min) (Ward, Judge and Corall,

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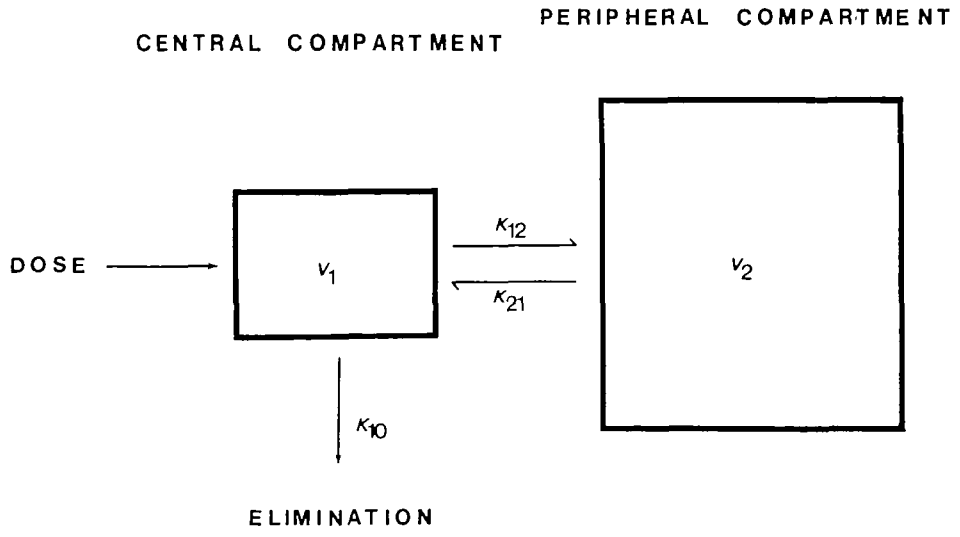

FIG. 2. Schematic diagram of the two-compartment open model.

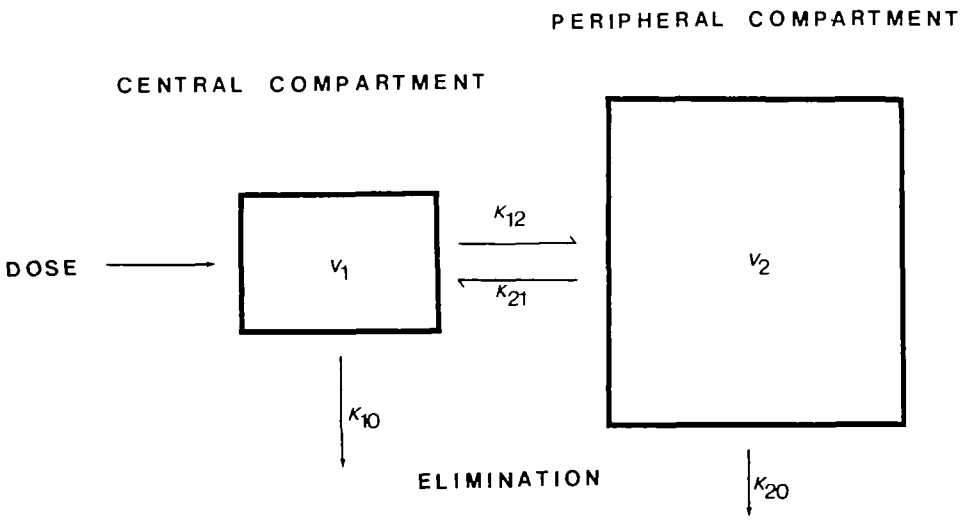

FIG. 3. Schematic diagram of the two-compartment open model for atracurium.

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1982; McLeod, Watson and Rawlins, 1976). The total clearance of 5.5 ml min^{-1} kg^{-1} was significantly greater than that for pancuronium. The small "apparent" volume of distribution (V_{area}) probably implies that there was very little tissue binding of the drug.

Investigations in animals and *in vitro* studies have shown that the elimination of atracurium is mainly by non-enzymatic Hofmann decomposition (Hughes and Chapple, 1980). This unique method of elimination of a neuromuscular blocking drug, though useful in clinical practice, created two major problems for this study. The first was that of the continuing degradation of atracurium after the withdrawal of the blood sample. To overcome this, the time between the sampling and the freezing of the plasma was kept to a minimum. Plasma was separated by ultra-rapid centrifugation (in less than 30 s) in the operating theatre and frozen immediately. Samples were then extracted for HPLC analysis within 24 h.

The second problem was which pharmacokinetic model to use. The programme used initially to determine the shape of the decay curve and to convert it into components (or compartments) of an exponential equation was unbiased and attempted to fit up to a five-compartment model (Provencher, 1976). A two-component fit was always preferred and this was confirmed by eye. This two-compartment open model was described by Greenblatt and Koch-Weser (1975) and is represented in figure 2. In this model all elimination is from the central compartment and the microkinetic variables (k_{12}, k_{21}) can be determined. As stated, the non-enzymatic breakdown of atracurium is by Hofmann elimination and this is not predominantly confined to the central compartment. The model for atracurium is better represented by figure 3 where k_{10} is the elimination rate constant from the central compartment and k_{20} is the elimination rate constant from the peripheral compartment. From this model it is not possible to determine the microkinetic parameters, so the values for clearance and total volume of distribution are derived directly from the macrokinetic parameters (A, α, B, β) using the "area under the curve".

In conclusion atracurium has a relatively short and reproducible elimination half-life and a small volume of distribution. This makes it useful for short operative procedures, but more importantly might make it an ideal drug for administration by continuous infusion.

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PHARMACOCINETIQUE DU BESYLATE D'ATRACURIUM CHEZ DES SUJETS EN BONNE SANTE (APRES UNE DOSE UNIQUE INTRAVEINEUSE DIRECTE)

RESUME

La décroissance plasmatique du besylate d'atracurium a été étudiée dans deux groupes de six patients. Le groupe I a reçu 0,6 mg kg^{-1} d'atracurium et le groupe II 0,3 mg kg^{-1} en une dose inique intraveineuse directe. Les concentrations plasmatiques étaient mesurées par HPLC (chromatographie liquide de haute performance). Un modèle pharmacocinétique individuel à deux compartiments a été utilis pour l'interprétation. Les résultats des deux groupes n'étaient pas significativement différents, donnant des valeurs moyennes globales de 2 min ± 0,2 ESM pour la demi-vie de distribution ($T_{\frac{1}{2}}^{\alpha}$), 19,9 min ± 0,6 pour la demi-vie d'élimination ($T_{\frac{1}{2}}^{\beta}$), 5,5 ml min^{-1} kg^{-1} ± 0,2 pour la clairance totale (Cl) et 157 ml kg^{-1} ± 7 pour le volume total de distribution (V_{aire}).

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PHARMAKOKINETIK VON ATRACURIUM-BESYLAT BEI GESUNDEN PATIENTEN (NACH EINER EINZELNEN INTRAVENÖSEN BOLUSGABE)

ZUSAMMENFASSUNG

Die Plasmakonzentrationsabnahme von Atracurium-besylat wurde bei zwei Gruppen von je sechs Patienten untersucht. Gruppe I erhielt 0,6 mg kg^{-1} Atracurium, Gruppe II 0,3 mg kg^{-1} als einzelne intravenöse Bolusgabe. Die Plasmakonzentrationen wurden mit Hochleistungs-Flüssigkeitschromatographie gemessen. Ein individuelles pharmakokinetisches Zwei-Kompartimente-Modell wurde zur Interpretation verwendet. Die Ergebnisse beider Gruppen waren nicht signifikant unterschiedlich. Die Mittelwerte lagen bei 2 Minuten (±0,2 "standard error") für die Verteilungs-Halbwertszeit ($T\frac{1}{2}^{\alpha}$), 19,9 Minuten (±0,6) für die Eliminations-Halbwertszeit ($T\frac{1}{2}^{\beta}$) 5,5 ml min^{-1} kg^{-1} (±0,2) für die totale Clearance und 157 ml^{-1} kg^{-1} (±7) für das totale Verteilungsvolumen (V_{area}).

FARMACOCINÉTICA DEL BESILATO DE ATRACURIO EN PACIENTES SANOS (DESPUÉS DE UNA DOSIS DE BOLO I.V. ÚNICA)

SUMARIO

Se examinó la descomposición plasmática del besilato de atracurio en dos grupos de seis pacientes. Al Grupo I, se le administró 0,6 mg kg^{-1} de atracurio y al Grupo II 0,3 mg kg^{-1} por medío de una dosis i.v. de bolo única. Se midieron las concentraciones en el plasma por medio de una cromatografía de líquido de alto rendimiento. Para la interpretación, se usó un modelo farmacocinético individual de dos compartimientos. No diferían de manera significante los resultados obtenidos con los dos grupos, con valores globales promedios de 2 min (±0,2 SEM) para la media-vida de distribución ($T_{\frac{1}{2}}^{\alpha}$), 19,9 min (±0,6) para la media-vida de eliminación ($T_{\frac{1}{2}}^{\beta}$), 5,5 ml min^{-1} kg^{-1} (±0,2) para la eliminación total (*Cl*) y 157 ml kg^{-1} (±7) para el volumen total de distribución (V_{area}).

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