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PHARMACOKINETICS OF PROPOFOL (DIPRIVAN) IN ELDERLY PATIENTS

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SUMMARY

The pharmacokinetics of propofol (2,6 diisopropylphenol) were compared in 12 patients aged 65–80 yr and 12 patients aged 18–35 yr. After premedication with papaveretum i.m., anaesthesia was induced with propofol 2.0 mg kg^{-1} in the elderly and 2.5 mg kg^{-1} in the younger patients. Alcuronium 12–20 mg was then given and the patient's lungs ventilated with halothane and nitrous oxide in oxygen. Blood was taken after various time intervals up to 24 h for the measurement of propofol concentrations by HPLC and for the estimation of propofol protein binding. The mean blood propofol concentration was generally higher in the elderly group, but this difference was only significant at 2 min after induction. The clearance of propofol was significantly lower in the elderly (1.44 ± 0.10 (SE) litre min^{-1}) than in the younger patients (1.79 ± 0.12 litre min^{-1}). The volume of the central compartment in the elderly patients was significantly smaller (19.6 ± 5.2 litre) than that in the young (26.3 ± 2.9 litre). There was no difference in the volume of distribution at equilibrium (1608 ± 246 litre in the elderly and 1757 ± 360 litre in the young), in the volume of distribution at steady state (691 ± 139 litre in the elderly and 771 ± 236 litre in the young) or in the half-lives of distribution and elimination. The plasma protein binding of propofol was similar in both groups and showed no trend with time after dose.

In elderly patients there is a tendency for total body water, cardiac output and hepatic blood flow to be lower than in young patients [1]. Pharmacokinetic studies of thiopentone [2, 3] methohexitone [4] and etomidate [5] have shown significant changes with ageing. We have compared the pharmacokinetics of propofol (2,6 diisopropylphenol) in elderly and young patients.

PATIENTS AND METHODS

Twenty-four patients were studied: 50% were aged 65–80 yr, the remainder being 18–35 years old. All patients were ASA grade I–II and gave informed consent to the study. All patients underwent surgery under general anaesthesia. Hospital Ethical Committee approval was obtained.

Patients were premedicated with papaveretum 10–20 mg i.m. 1 h before surgery; hyoscine 0.2–0.4 mg was given if an anti-sialagogue was indicated. An 18-gauge cannula (for venous sampling) was inserted to a vein in the antecubital fossa. A 23-gauge "Butterfly" needle was placed in a vein on the dorsum of the contralateral hand for administration of drugs. Anaesthesia was induced with the aquaeous emulsion formulation of propofol (Diprivan) 2.5 mg kg^{-1} in the younger patients and 2.0 mg kg^{-1} in the elderly patients; the injection was given over 30 s. Time 0 was taken to be when the injection was completed.

When present, the severity of pain on injection of propofol was noted, and the intensity was assessed as mild, moderate or severe. Any evidence of excitatory phenomena on induction of anaesthesia was recorded. When anaesthesia had been induced successfully 67% nitrous oxide and 0–1% halothane in oxygen were administered using an anaesthetic face mask. Alcuronium

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12.5–20 mg was given and when muscle paralysis was satisfactory the trachea was intubated; the patients' lungs were then ventilated to normocapnoea according to the Radford nomogram. No other drugs were given during the operation. At the end of surgery neostigmine 2.5 mg was given (with atropine 1.2 mg) to antagonize neuromuscular blockade. During anaesthesia the arterial pressure and heart rate were monitored. Papaveretum and prochlorperazine were given, when necessary, in the postoperative period.

Blood was taken for whole blood propofol estimation before injection, and after the end of the propofol injection at the following times: 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120 and 150 min and 3, 4, 5, 6, 7, 8, 10, 12, 18 and 24 h. Each 5-ml sample was thoroughly mixed in tubes containing potassium oxalate and stored at +4 °C until assayed. Additional blood samples (10 ml) were taken approximately 10 and 120 min following the injection for estimation of propofol plasma protein binding. After thorough mixing in tubes containing potassium oxalate, these samples were centrifuged, the plasma removed and stored in plain tubes at +4 °C until required for analysis.

Propofol concentrations in the samples of blood and plasma were determined by a modification of the method described by Adam and colleagues [6]. The cyclohexane extract was basified with tetramethylammonium hydroxide and then evaporated to dryness under nitrogen. After reconstitution, the residue was subjected to high pressure liquid chromatography with fluorescence detection. The limit of detection was 2 ng ml^{-1} with an interbatch coefficient of variation of 8% over the concentration range observed in this study.

Pharmacokinetic analysis of each data set was performed using the extended least squares curve fitting programme ELSFIT [7]; initial parameter estimates were derived using STRIPE [8].

The degree of binding of propofol to plasma proteins was estimated using a "Dianorm" equilibrium dialysis apparatus. Aliquots of plasma (1 ml) were dialysed for 4 h against 1 ml of phosphate buffer 0.067 mol $litre^{-1}$, pH 7.4, containing 0.9% w/v sodium chloride. Weighed aliquots of dialysis buffer were then analysed for propofol content using the method described for whole blood.

The blood propofol concentrations at each time interval and the derived pharmacokinetic parameters were found (by plotting the data on Normal distribution paper) to follow a skewed distribution. Therefore, we used a non-parametric test (the Wilcoxon Rank Sum Test) to determine the significance of differences between the two groups; the minimum level of statistical significance was taken as $P < 0.05$.

RESULTS

The demographic details of the two groups of patients are shown in table I.

Anaesthesia was induced smoothly in all patients. Excitatory phenomena were not seen and there were no involuntary muscle movements. Mild or moderate pain on injection was experienced by three elderly and four of the younger patients; only one patient (from the younger group) considered the pain to be severe. Hypotension (systolic arterial pressure less than 90 mm Hg following induction) occurred in three elderly and one young patient; change in posture and a decrease in the inspired halothane concentration brought about a satisfactory increase in arterial pressure in these patients. All patients recovered swiftly and smoothly from anaesthesia which lasted on average 43 min (range 24–61, SD 11.6 min) in the elderly patients and 45 min (16–140, SD 35.2 min) in the younger group.

Blood concentrations of propofol in the elderly patients were compared after dose correction (by a factor of 5/4) with those in the young. At 2 min after the injection the mean blood concentration of propofol was 6.07 ± 1.08 SEM $\mu g\ ml^{-1}$ in the elderly patients and $4.15 \pm 0.42\ \mu g\ ml^{-1}$ in the younger group ($0.01 < P 0.02$). There were no other significant differences in mean blood propofol concentrations at any time. Figure 1 shows the dose-corrected mean blood propofol concentrations for the two groups.

After visual inspection of the plotted data for each individual a three-compartment open mammalian model with excretion from the central compartment was fitted to each data set. For two elderly patients only two exponential phases could be defined with any confidence and the data for

TABLE I. *Age, weight and height of patients (mean ± 1 SD)*

	Age (yr)	Weight (kg)	Height (m)
Elderly	71.4 ± 4.03	61.8 ± 9.7	1.61 ± 0.09
Young	27.5 ± 5.25	65.7 ± 10.3	1.72 ± 0.08
		ns	$P < 0.05$

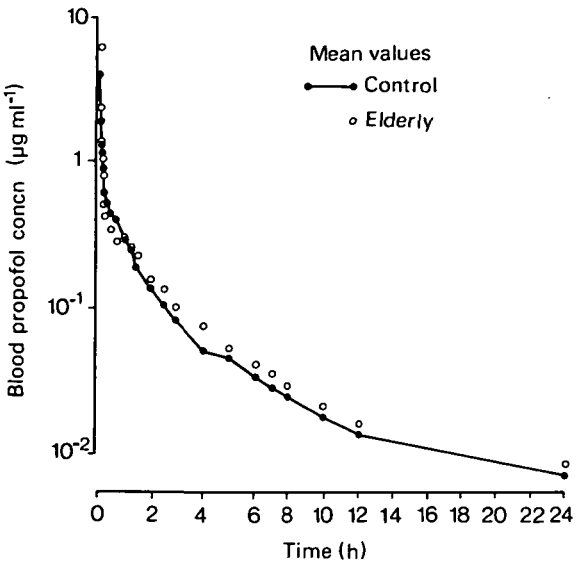

FIG. 1. Mean blood propofol concentrations for young patients and elderly patients after dose correction.

these patients were assumed to conform to a two-compartment model. The half-lives of the three phases ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$) the total body clearance (TBC), the volumes of distribution at steady state (V^{ss}) and equilibrium (V^{γ}) and the volume of the central compartment (V) were then calculated using standard equations [9]. As the data were not normally distributed, the Wilcoxon Rank Sum Test was applied for the statistical analysis. The results are shown in table II.

The volume of the central compartment was significantly smaller ($P = 0.046$) in the elderly (19.6 ± 5.2 litre) than in the younger (26.3 ± 2.9 litre) patients. The total body clearance of propofol was considerably lower in the elderly (1.44 ± 0.10 litre min^{-1}) than the young (1.79 ± 0.12 litre min^{-1}) and this difference was also significant ($P = 0.03$). However, when individual data for V and TBC were normalized for body weight there were no statistically significant differences between the two groups. There was no statistical difference in the other pharmacokinetic parameters.

Propofol concentrations in whole blood for individual patients in both groups were similar to those in plasma at the same sampling time. Mean ratios (plasma:whole blood) at 10 min after induction were 1.23 ± 0.11 and 0.97 ± 0.08 for elderly and young patients, respectively. Corresponding ratios at 120 min after induction were 1.47 ± 0.21 and 1.12 ± 0.09.

Propofol protein binding was high: values of 97–99% were obtained at both sampling times. There was no significant difference in protein binding between the elderly and young patients at either sampling time, and there was no apparent trend in the data with time after dose.

DISCUSSION

The pharmacokinetic data for the younger patients show that, while the total body clearance

TABLE II. *Volumes of distribution at steady state* (V^{ss}) *and equilibrium* (V^{γ}); *volume of central compartment* (V); *total body clearance (TBC) and half-lives of the three phases* ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$); *rate constants (mean values ± 1 SEM)*

	Young	Elderly	P
V^{ss} (litre)	771 ± 236	691 ± 139	ns
V^{γ} (litre)	1756 ± 360	1608 ± 246	ns
V (litre)	26.3 ± 2.9	19.6 ± 5.2	0.046
TBC (litre min^{-1})	1.78 ± 0.12	1.43 ± 0.09	0.030
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.04 ± 0.27	1.84 ± 0.25	ns
$T_{\frac{1}{2}}^{\beta}$ (min)	52.4 ± 9.2	69.3 ± 8.7	ns
$T_{\frac{1}{2}}^{\gamma}$ (min)	674 ± 122	834 ± 170	ns
V^{ss} (litre kg^{-1})	11.9 ± 3.5	12.4 ± 3.3	ns
V^{γ} (litre kg^{-1})	27.1 ± 5.4	28.4 ± 6.0	ns
V (litre kg^{-1})	0.415 ± 0.055	0.311 ± 0.080	ns
TBC (ml min^{-1} kg^{-1})	27.7 ± 2.3	23.2 ± 1.1	ns
k_{31}	$(1.91 \pm 0.2)10^{-3}$	$(1.63 \pm 0.21)10^{-3}$	ns
k_{10}	$(0.77 \pm 0.09)10^{-1}$	$(1.23 \pm 0.26)10^{-1}$	ns
k_{13}	$(3.91 \pm 0.58)10^{-2}$	$(5.83 \pm 1.19)10^{-2}$	ns
k_{12}	$(2.46 \pm 0.40)10^{-1}$	$(2.95 \pm 0.79)10^{-1}$	ns
k_{21}	$(5.97 \pm 0.97)10^{-2}$	$(3.75 \pm 0.51)10^{-2}$	ns

was very large (mean 1.79 litre min^{-1}), $T_{\frac{1}{2}}^{\gamma}$ was prolonged (mean 674 min), so resulting in a high equilibrium volume of distribution estimate. The mean volume of distribution at steady state was less than half the value for the equilibrium volume of distribution. This suggests that, after a rapid injection of a single dose of propofol, the drug was rapidly cleared from the body, but a small proportion remained in tissue (presumably lipid) and was eliminated much more slowly. It is likely, therefore, that the elimination of propofol during the third exponential phase is constrained by its slow return from the deep to the central compartment. This is confirmed by mean ratios of $k_{31}:k_{10}$, which were 0.0264 ± 0.0029 (SEM) for the young patients and 0.0218 ± 0.0064 for the elderly patients. Elimination during the second exponential phase is probably dominated by the unconstrained metabolic clearance of propofol. Compared with previously published data in patients [10–12] we found the third exponential phase half-life to be relatively prolonged (674 compared with 184–382 min), whereas the half-lives for the first two phases were broadly similar. This difference was probably a consequence of the longer sampling period in our study—previous studies had only sampled for 8–12 h—so enabling the parameters of the third phase to be determined with more confidence. However, even in the present study the sampling period was shorter than desirable (only about double $T_{\frac{1}{2}}^{\gamma}$).

The reduction in dose requirements of thiopentone in elderly patients has been well documented [13]; a similar phenomenon is recognized for other i.v. induction agents. It would, therefore, be surprising if the same did not hold true for propofol and, in fact, more recent work [14, 15] confirmed that the propofol dose requirements are also age-related.

We found that the initial blood concentration of propofol (at 2 min) was significantly higher in the elderly than the younger patients. This was a consequence of the significantly lower initial distribution volume in the elderly, which is consistent with a reduction in the volume of highly perfused tissues relative to body mass or a reduced perfusion of these tissues as a consequence of the documented [1] lower cardiac output in elderly patients. Similar trends have been observed for thiopentone [2] and etomidate [5], but no age-related differences in V were seen for fentanyl and alfentanil [16]. The relatively high blood concentrations of propofol in the first few minutes following induction of anaesthesia could be implicated in the higher incidence of hypotension which we found in the elderly as compared with the younger patients.

Results from a volunteer study [17] in which a subanaesthetic dose of ^{14}C-propofol was administered suggested that propofol is extensively metabolized before renal elimination—only 0.3% of the material recovered from the urine was present as unchanged drug. Hence renal clearance would be expected to play little part in the total body clearance of propofol; an interim analysis of a study of the kinetics of propofol in patients with renal failure [18] showed no significant difference in the clearance of propofol in these patients as compared with controls. Our work has resulted in values for total body clearance which approximate to hepatic blood flow. The values for the elderly (1.44 ± 0.10 litre min^{-1}) were significantly lower than those for the controls (1.79 ± 0.12 litre min^{-1})—the age-related decline in hepatic blood flow [19] results in reduced total body clearance of drugs, like propofol, which depend heavily on hepatic metabolism for their elimination.

Similarly, the clearance of etomidate has been shown to be significantly decreased with age, with a decrease of approximately 2 ml kg^{-1} min^{-1} for every decade increase in the 22–82 yr age range. However, thiopentone, the clearance of which is capacity limited, showed no change in clearance with age [2, 3]. The difference (25%) in the volume of the central compartment for propofol, between the elderly and young patients, is consistent with the reduced induction dose requirement in the former observed by Dundee and colleagues [14]. Furthermore, the 20% reduction in total body clearance observed in the elderly patients would be expected to result in a slightly smaller propofol maintenance dose requirement in the elderly. Mackenzie and Grant [20] have shown recently that patients older than 65 yr receiving an infusion of propofol for about 1.5 h required an infusion rate significantly less (24%) than that required by younger subjects.

Although mean values of V normalized for body weight were also 25% lower in elderly patients, the difference was not statistically significant. Similarly, body weight normalized values of TBC were 16% lower in elderly patients, but the difference did not reach statistical significance. The reason for this is unclear, but may be the slightly greater inter-individual variability in the data when normalized for body weight.

In conclusion, our work has shown that the initial distribution volume of propofol was lower in elderly compared with younger patients and, as a consequence, propofol concentrations were higher in the elderly immediately following injection. Additionally, the total body clearance of propofol in the elderly was lower than that in the younger patients. These pharmacokinetic differences could be explained by decreases in cardiac output and hepatic blood flow in the elderly.

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