

EFFECT OF SPEED OF INJECTION ON INDUCTION OF ANAESTHESIA USING PROPOFOL

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2,6-Diisopropylphenol (ICI 35 868), a drug initially formulated in Cremophor EL (disopropofol) is now prepared as an emulsion (propofol). Both formulations have been used to induce and maintain anaesthesia in animals, their dose requirements and anaesthetic properties being similar (Glen and Hunter, 1984). However, studies with the Cremophor formulation in animals (Glen, 1980) and in man (Rolly, Versichelen and Zubair, 1980a, b) showed that the dose required and the speed of onset of anaesthesia were affected by changes in the rate of injection. Briggs and colleagues (1981) used the Cremophor formulation and found that anaesthesia was induced in one arm-brain circulation time when the drug was given rapidly during reactive hyperaemia.

The aim of the present study was to examine the effect of using three different rates of injection on the efficacy and incidence of side effects of the emulsified formulation, when used to induce anaesthesia in unpremedicated patients.

PATIENTS AND METHODS

A single dose of propofol 2 mg kg⁻¹ i.v. was given to 60 unpremedicated informed patients, ASA class I or II, with an age range from 18 to 65 yr. An equal number of 30 patients of each sex were randomized to receive the injection of 1% propofol in emulsion over 5, 20 or 60 s. The study was approved by the Ethics Committee of the Hospital.

Before the induction of anaesthesia an infusion of 5% dextrose solution was commenced, via a cannula in a forearm vein. When the propofol was to be given in 5 s a three-way tap was included in the infusion line, so that the drug could be given

SUMMARY

Sixty unpremedicated patients (30 male) were randomly allocated to three groups. They received an induction dose of propofol 2 mg kg⁻¹ over 5, 20 or 60 s to a forearm vein. Anaesthesia was maintained with conventional inhalation anaesthetic agents. Anaesthesia was induced satisfactorily in all 20 of the patients in the 5-s group, in 19 of the patients in the 20-s group and in 18 of the patients in the 60-s group. The rate of injection had a significant influence on induction time. Mean induction time increased from 21.5 to 34.7 and 50.5 s, when injection time was increased from 5 to 20 to 60 s, respectively. Similar induction times were found in male and female patients. There was no significant difference between the groups, in depth of anaesthesia obtained — as assessed by the eyelash reflex. Mean arterial pressure decreased to the same extent in all three groups. Two minutes after induction, mean systolic arterial pressure was reduced by 15.1, 13.5 and 19.3 mm Hg in the 5-, 20- and 60-s groups, respectively, and mean diastolic arterial pressure by 10.3, 13.2 and 13.7 mm Hg. Heart rate changes were insignificant. Apnoea of more than 10 s duration was seen frequently in all three groups, but the results suggest that the incidence was not influenced by the rate of injection. Three patients experienced mild pain at the time of injection. No major adverse reactions occurred during or after anaesthesia.

directly into the cannula, and flushed through rapidly. When the propofol was administered more slowly, it was injected to the rapidly running infusion. The full scheduled dose of propofol was given even if anaesthesia was induced before the injection was completed. If anaesthesia was not induced, as assessed by the

patient failing to stop counting 60 s after the end of the injection of the propofol, a different anaesthetic was administered. Two minutes after the completion of the injection of propofol, anaesthesia was maintained with inhalation agents, and neuromuscular blocking drugs were administered to facilitate controlled ventilation.

The induction time was taken as the interval from the start of the injection to the point at which the patient stopped counting. Anaesthesia was deemed to have been induced successfully if the patient stopped counting within a period of 60 s following the completion of injection. In addition, the presence or absence of an eyelash reflex was recorded 60 s after completion of the injection.

Apnoea was defined as loss of spontaneous breathing for any period of time greater than 10 s.

Heart rate, derived from the ECG, and systolic and diastolic arterial pressures (Riva-Rocci method) were recorded before and 1, 2 and 5 min after completion of the injection of propofol.

Side effects occurring during the induction of anaesthesia were recorded, and an overall assessment of the quality of induction obtained.

TABLE I. Demography of patients (mean values \pm SD)

	Duration of injection of propofol		
	5 s	20 s	60 s
Age (yr)	38.3 \pm 14.1	38.5 \pm 14.1	35.8 \pm 16.0
<i>n</i>	20	20	20
Weight (kg)			
Males	71.3 \pm 8.3	71.9 \pm 9.6	68.8 \pm 9.3
<i>n</i>	10	10	10
Females	61.0 \pm 7.4	65.6 \pm 11.95	62.9 \pm 7.5
<i>n</i>	10	10	10
Height (cm)			
Males	173.5 \pm 7.5	176.4 \pm 7.6	174.6 \pm 8.1
Females	163.6 \pm 7.2	164.2 \pm 5.7	161.4 \pm 3.6

TABLE II. Systolic and diastolic arterial pressures (mean values \pm SD) in all patients in whom anaesthesia was induced with propofol 2 mg kg⁻¹, with injections of 5 s, 20 s or 60 s duration

	Systolic pressure (mm Hg)			Diastolic pressure (mm Hg)		
	5 s	20 s	60 s	5 s	20 s	60 s
Baseline	124.9 \pm 12.7	126.8 \pm 18.9	127.2 \pm 19.2	75.1 \pm 10.2	81.4 \pm 10.2	75.8 \pm 13.7
<i>n</i>	20	19	18	20	19	18
1 min after induction	112.4 \pm 17.0	112.9 \pm 18.6	117.5 \pm 21.5	68.2 \pm 9.9	70.1 \pm 11.6	69.6 \pm 16.9
2 min after induction	109.8 \pm 18.3	113.3 \pm 19.0	107.9 \pm 12.6	64.8 \pm 7.4	68.3 \pm 12.7	62.2 \pm 15.1
5 min after induction	123.1 \pm 20.3	124.4 \pm 28.3	114.1 \pm 23.6	80.5 \pm 16.5	77.9 \pm 17.6	71.4 \pm 21.4

Statistical significance was assessed by analyses of variance for induction time, arterial pressure and heart rate; by multi-dimensional contingency table for abolition of eyelash reflex and by a multi-variate rank test for apnoea.

RESULTS

Mean ages, weights, heights and sex of the patients in the three groups are given in table I. No statistical differences were evident between the groups.

Anaesthesia was induced successfully in all of the patients in the 5-s group, but was not induced in one patient (male) in the 20-s group (95% success) and in two patients (male) in the 60-s group (90% success).

The mean (\pm SD) induction time of 21.5 (\pm 5.5) in the 5-s group was significantly shorter ($P < 0.001$) than the time of 34.7 s (\pm 8.6) in the 20-s group, and the latter was significantly shorter ($P < 0.001$) than the time of 50.5 s (\pm 11.4) in the 60-s group. There was no significant difference in the responses between males and females within the same group.

The eyelash reflex was abolished in 80% of the patients in the 5-s group, in 70% of the patients in the 20-s group and in 50% of the patients in the 60-s group. If the patients in whom anaesthesia was not induced are excluded, these figures become 80%, 74% and 56%, respectively. Despite this trend, there was no statistically significant influence of speed of injection or sex on the abolition of the eyelash reflex.

Mean systolic and diastolic arterial pressures decreased ($P < 0.05$) in all three groups after the induction of anaesthesia (table II). The greatest effect was noted 2 min after injection, when mean systolic arterial pressure was decreased by 15.1, 13.5 and 19.3 mm Hg for the 5-, 20- and 60-s

TABLE III. Number of patients with apnoea at induction after injection of propofol 2 mg kg⁻¹ over 5 s, 20 s or 60 s

	5 s		20 s		60 s	
	Male	Female	Male	Female	Male	Female
No apnoea or < 10 s	1	2	3	3	2	4
10-30 s	3	5	0	0	5	2
30-60 s	6	2	7	6	2	4
> 60 s	0	1	0	1	1	0

groups, respectively, and mean diastolic pressure by 10.3, 13.2 and 13.7 mm Hg, respectively. However, there were no statistically significant differences between the groups at any time. Little change in heart rate occurred within the first 5 min after injection and no significant differences were observed.

After the induction of anaesthesia, apnoea was observed in 17 patients in the 5-s group, and in 14 patients in both the 20-s and 60-s groups (table III). No statistically significant differences were demonstrated between the three groups with respect to the incidence or duration of apnoea. In one patient after the injection of propofol in 5 s, a period of apnoea of 16 s was recorded, followed by one gasping breath and a further period of apnoea lasting 84 s.

Excluding those administrations in which anaesthesia had lightened to the extent of being unsatisfactory before the end of the agreed time of observation (2 min) with each injection rate, induction was graded as poor in one patient, because of prolonged apnoea, spontaneous movement and spasticity in the 5-s, 20-s and 60-s groups, respectively. In all other patients induction of anaesthesia was graded as good or adequate.

The incidence of side effects occurring during induction is shown in table IV. Some of the side effects recorded were probably the result of light anaesthesia.

DISCUSSION

With the previous Cremophor formulation of 2,6-diisopropylphenol (disopropofol) it was shown, in man, that 2 mg kg⁻¹ was a satisfactory dose with which to induce anaesthesia (Briggs et al., 1981) and that the speed of onset of anaesthesia was affected by the rate of injection (Rolly, Versichelen and Zubair, 1980b). In the present study with 2 mg kg⁻¹ of the new emulsified formulation (propofol), there was a decrease in induction time with decreasing duration of injection from 60 s, to 20 s, to 5 s. In animal studies with the emulsion formulation, hypnotic activity in male rats was marginally less than that in female animals (Glen and Hunter, 1984). If this difference existed in patients, the induction time would have been expected to be more rapid in the female patients. This was not observed in the present study. Although, in each group, the female patients had a shorter induction time than male subjects, the differences were never significant.

An indication that deeper anaesthesia was achieved with the faster injection was seen in the assessment of loss of eyelash reflex, although the differences between the three groups were not significant.

Anaesthesia was induced in all patients in the 5-s group, but with the longer injection times anaesthesia was not induced in a small number of male patients. These findings are similar to our previous results using the Cremophor formulation, whereby with disopropofol 1.5 mg kg⁻¹ given at an injection speed of 10 or 20 s, all patients were successfully anaesthetized, but the eyelash reflex was abolished in only 62% of patients (Rolly, Versichelen and Zubair, 1980b). The failure to induce anaesthesia in a small number of patients with 2.0 mg kg⁻¹ of the emulsion formulation suggests a marginal reduction in potency in comparison with the earlier Cremophor formulation. In the present study, all patients were not

TABLE IV. Number of patients with side effects at induction following propofol 2 mg kg⁻¹. * Possibly related to inadequate depth of anaesthesia

Speed of injection	Spontaneous movement	Hypertonus	Cough	Laryngospasm	Flush/rash	Pain on injection	Other
5 s	2	0	3	1	0	2	1
20 s	1	0	1	0	2	1	1*
60 s	1*	1	2	0	1	0	

premedicated deliberately. Probably, the addition of premedication would have changed the present findings in regard to incidence and rate of onset of anaesthesia.

Decreases in arterial pressure and the incidence of apnoea were similar in all three groups. There was little change in heart rate. These findings are of interest as it was anticipated that the 5-s rate of injection would have been associated with a greater degree of cardiorespiratory depression and that depressant effects would have been minimized using the slowest rate of injection.

The incidence of side effects was low in all groups and was not influenced by the rate of injection.

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