

PROLONGED SEDATION WITH PROPOFOL IN ICU PATIENTS: RECOVERY AND BLOOD CONCENTRATION CHANGES DURING PERIODIC INTERRUPTIONS IN INFUSION

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Agitated, restless ICU patients may require prolonged, rapidly controllable periods of sedation. The agents used should permit rapid recovery on periodic cessation of administration in order to allow regular clinical assessments, especially of neurological status.

Since Althesin has been discontinued, a suitable agent is still not available [1]. The use of etomidate led to an increase in mortality because of its adrenocortical suppressive effects [2, 3].

Sedation by continuous infusion of midazolam in ICU patients may lead to accumulation and prolonged recovery [4, 5]. Periodic antagonism of midazolam sedation with flumazenil is under evaluation.

Interest in propofol as a sedative agent is increasing. Previous studies assessed sedation of less than 24 h duration [6, 7]. The present study was carried out to determine if a continuous infusion of propofol provided convenient sedation over 4 days. In order to determine the risk of drug cumulation with prolonged infusion, recovery times and blood concentration profiles have been compared, following cessation of the infusion at 24, 48, 72 and 96 h.

PATIENTS AND METHODS

The study, approved by the Ethics Committee of the Medical Faculty, was carried out on 14 adults

SUMMARY

Propofol (mean dose 2.85 mg kg⁻¹ h⁻¹) was administered for 4 days by continuous i.v. infusion for sedation in 14 agitated and restless ICU patients. This provided rapid control of the level of sedation. When the infusion was discontinued, adequate recovery with response to commands was obtained in most patients by 10 min. Recovery times and the decrease in blood propofol concentration were similar after 24, 48, 72 and 96 h of infusion. Cumulative effects, tachyphylaxis, or other untoward effects were not observed.

treated in a surgical ICU for trauma with or without postoperative complications. Informed consent was given by the family.

Inclusion criteria were excessive and prolonged mental and motor activity related to head injury, alcoholism, metabolic disorders, hypoxia, anxiety and sleep deprivation. Exclusion criteria included simultaneous administration of agents which might modify the activity of propofol or the patient's neurological status (hypnotics, analgesics, muscle relaxants), major hepatic failure, shock and increased intracranial pressure (excluded by a Glasgow coma scale score more than 8 and lack of evidence for increased ICP at CT scanning) in trauma patients. All patients were undergoing artificial ventilation via a nasotracheal tube.

Undiluted propofol was infused continuously using syringe pump over 4 days via a central venous catheter. The initial dose was determined arbitrarily as 2 mg kg⁻¹ h⁻¹. A loading dose was

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not administered. At the end of each subsequent hour the infusion was increased or decreased by $0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$ until a suitable level of sedation was reached. The rate was kept constant thereafter.

The level of sedation was scored using the six-grade scale devised by Ramsay and colleagues [1]: 1 = anxious and agitated or restless or both; 2 = co-operative, orientated and tranquil; 3 = responds to commands only; 4 = asleep with brisk response to light glabellar tap or loud auditory stimulus; 5 = asleep with a sluggish response to stimulus; 6 = asleep with no response to stimulus.

The propofol infusion was stopped transiently for 90 min at 24, 48 and 72 h after commencement, and discontinued after 96 h. During these four interruptions, the speed of recovery was assessed and blood samples taken simultaneously.

Propofol concentrations in whole blood were measured by high pressure liquid chromatography (HPLC) using fluorescence detection (emission and excitation wavelengths at 310 nm and 276 nm, respectively). The HPLC system (Waters) included a hypersil 3 ODS reversed column. The lower limit of detection was $0.1 \mu\text{g ml}^{-1}$ and the coefficient of variation averaged 4.1 per 100 within assay estimations. The response was linear in the concentration range of $0.5\text{--}4 \mu\text{g ml}^{-1}$. Each value was the mean of two assays per sample.

The safety of propofol infusion was assessed by routine haemodynamic monitoring which included measurement of systemic arterial pressure and heart rate using a Dinamap.

In order to assess the severity of illness, the Apache II score was calculated in each patient, using the worst values in the 24-h period before starting propofol [8]. The Apache II score at admission was not considered because, in nearly all patients, sedation was not started until several days later. The data are expressed as mean (SEM) and compared using Mann-Whitney *U* test and Wilcoxon *T* test as appropriate.

RESULTS

Details of the 14 patients in the study are shown in table I.

At a mean rate of $2.85 (0.12) \text{ mg kg}^{-1} \text{ h}^{-1}$ continuous infusion of propofol provided a suitable level of sedation (grade 4 on the Ramsay scale) by 2–3 h after commencement. With increased experience, the time required to sedate adequately was reduced, and in otherwise healthy patients the propofol administration was started at a rate of $3 \text{ mg kg}^{-1} \text{ h}^{-1}$. A subsequent reduction in infusion rate was required in only one patient. The differences in infusion rates needed to produce comparable sedation between patients resulted partly from difficulty in obtaining the

TABLE I. Details of patients included in the study. MT = multiple trauma; CT = chest trauma; HT = head trauma; C = cirrhosis; POS = postorthopaedic surgery complication; DT = delirium tremens; COPD = chronic obstructive pulmonary disease; PAS = postabdominal surgery complication. *On day of starting sedation

Patient No.	Age (yr)	Sex	Weight (kg)	Diagnosis	Apache II score*	Dose		
						($\text{mg kg}^{-1} \text{ h}^{-1}$)	(ml day^{-1})	Total (g/4 days)
1	42	M	60	MT	20	3.0	432	17.3
2	81	M	65	CT	7	3.0	468	18.4
3	53	M	67	HT + C	12	1.4	225	9
4	23	M	57	HT	9	2.8	383	11.4 (3 days)
5	46	M	72	POS + DT	12	2.5	432	16.3
6	71	M	56	POS + COPD	8	2.9	389	15.4
7	52	M	80	PAS	12	3.0	576	23.0
8	53	M	86	MT + DT	7	3.1	648	25.9
9	19	M	50	MT	5	3.0	360	14.4
10	58	M	78	CT + DT	8	3.0	561	22.4
11	39	M	70	HT + DT	9	3.0	504	20.1
12	53	M	60	DT	20	3.0	432	17.3
13	53	F	60	MT	7	3.0	432	17.8
14	69	M	56	PAS + COPD	13	3.2	430	17.2
Mean						2.85	448	17.56
SEM						0.12	27.6	1.18

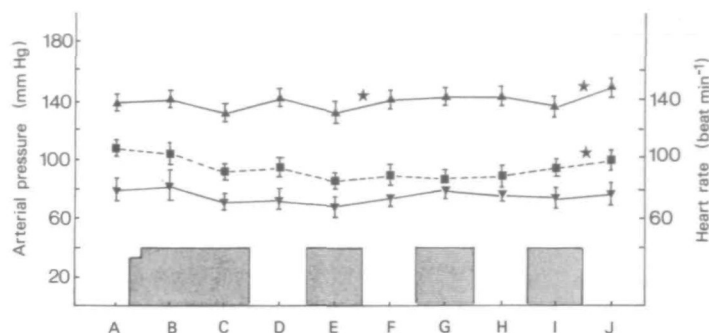


FIG. 1. Mean (SEM) values of systolic (▲) and diastolic (▼) arterial pressure and heart rate (■) before, during and after cessation of propofol infusion. Each shaded area corresponds approximately to a 24-h infusion. A = before commencing infusion; B = 1 h after starting the infusion; C = before stopping the 24-h infusion; D = 1 h after stopping the 24-h infusion; E = before stopping the 48-h infusion; F = 1 h after stopping the 48-h infusion; G = before stopping the 72-h infusion; H = 1 h after stopping the 72-h infusion; I = before stopping the 96-h infusion; J = 1 h after stopping the 96-h infusion. *Significant difference ($P < 0.05$) between two successive values.

TABLE II. Mean (SEM) values of biochemical and haematological variables before and after the 96-h administration of propofol

Variable	Before infusion		After infusion		P
Urea (mmol litre ⁻¹)	5.39	(0.98)	5.85	(1.08)	—
Creatinine (μmol litre ⁻¹)	96.9	(23.1)	93.8	(28.3)	—
Total bilirubin (μmol litre ⁻¹)	27.3	(5.15)	24.6	(4.31)	—
Conjugated bilirubin (μmol litre ⁻¹)	9.3	(2.6)	14.1	(4.9)	—
SGOT (u. litre ⁻¹)	139.4	(71.1)	43.1	(8.5)	—
SGPT (u. litre ⁻¹)	81.9	(42.8)	32.3	(9.7)	—
Prothrombin time (s)	13.5	(0.5)	13.2	(0.5)	—
Leucocytes ($\times 10^3$ mm ⁻³)	10.8	(1.5)	10.2	(1.1)	—
Platelets ($\times 10^3$ mm ⁻³)	169	(26)	208	(35)	—
Fibrinogen (g litre ⁻¹)	2.98	(0.37)	5.3	(0.57)	< 0.005

correct weight of the patients at the onset of sedation.

In 12 of 14 patients, the convenient infusion rate, determined during the initial few hours, was kept constant during 4 days. In patient No. 3, bleeding of oesophageal varices at 24 h resulted in decompensation of alcoholic cirrhosis and the need to decrease the infusion rate of propofol. Patient No. 4 recovered completely from post traumatic coma after 3 days sedation and the infusion was no longer required.

In all 14 patients, there was no evidence that prolonged infusion of propofol induced side effects sufficiently serious to justify cessation. All 14 patients survived admission to ICU, with the exception of patient No. 7, who died 10 days after the end of sedation. The cause of death was inoperable cancer of the gastrointestinal tract.

During sedation no major changes in cardiovascular (fig. 1), biochemical or haematological variables (table II) occurred.

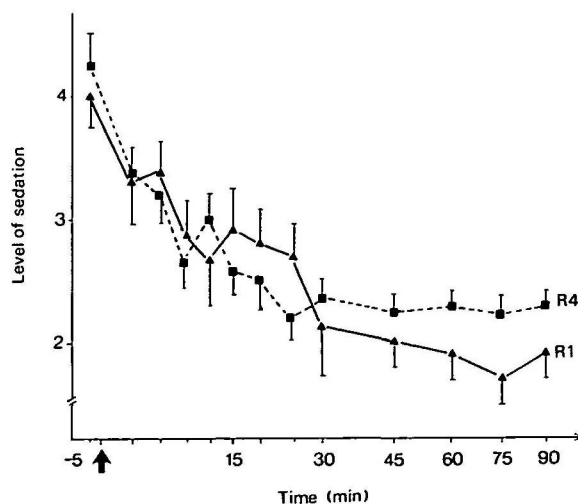


FIG. 2. Mean (SEM) changes in level of sedation (Ramsay score) after cessation of propofol infusion (arrow). -5 = Sedation level determined 5 min before end of infusion; R1 = changes after the 24-h infusion; R4 = changes after the 96-h infusion. Times on the x-axis are on a log scale.

TABLE III. Regression of sedation (Ramsay scores) and simultaneous decrease in blood concentrations of propofol after stopping the 24-h infusion (R1) and the 96-h infusion (R4). † Baseline values taken 5 min before discontinuation of infusion

Time (min)	Clinical recovery (Ramsay scores) (median (range))		Blood concentrations of propofol ($\mu\text{g ml}^{-1}$) (mean (SEM))	
	R1	R4	R1	R4
-5†	5.21 (5-2)	4.87 (5-2)	2.86 (0.29)	2.19 (0.19)
+2.5	4.2 (5-2)	3.85 (5-2)	1.91 (0.34)	1.54 (0.17)
+5	4.1 (5-2)	3.87 (4-2)	1.64 (0.28)	1.39 (0.12)
+7.5	3.5 (4-2)	2.20 (4-2)	1.46 (0.20)	1.15 (0.12)
+10	2.93 (5-1)	2.52 (4-2)	1.39 (0.23)	1.22 (0.11)
+15	3.40 (5-1)	3.1 (4-1)	1.19 (0.22)	1.18 (0.09)
+20	2.93 (5-1)	2.72 (5-2)	1.08 (0.17)	1.16 (0.09)
+25	2.81 (4-1)	2.62 (4-1)	1.17 (0.20)	1.09 (0.09)
+30	2.44 (4-1)	2.94 (3-2)	1.03 (0.17)	1.00 (0.09)
+45	2.37 (4-1)	2.51 (3-2)	0.96 (0.17)	0.93 (0.09)
+60	2.39 (4-1)	2.54 (3-2)	0.88 (0.15)	0.92 (0.09)
+75	2.26 (3-1)	2.36 (3-2)	0.92 (0.20)	0.81 (0.12)
+90	2.41 (3-1)	2.55 (3-2)	0.97 (0.22)	0.76 (0.12)

The circulation remained stable without the need for vasoactive agents or additional fluid load. Central venous pressure was monitored only when there had been an indication before starting sedation. During interruption of sedation, heart rate and arterial pressure tended to increase. In nearly all patients the colour of urine turned brown, sometimes mimicking porphyria.

When the infusion was stopped after 24 h the patients recovered rapidly (fig. 2, table III). Patients Nos 3 and 4, with head trauma, were unable to respond correctly to commands and were excluded, therefore, from clinical assessment of recovery. By 10 min, most patients (nine of 12) changed from level 4 to level 3 and responded adequately to commands. In one patient, agitation re-appeared. In the majority, the pupils dilated by 3-4 min. From 10 to 25 min most patients remained drowsy and several fell asleep again, but this "resedation" was transient and without clinical significance. After 30 min they were awake, but four of 12 were again highly agitated and restless.

The speeds of awakening after the 48-, 72- and 96-h infusions were similar. Resedation was less evident. Agitation and restlessness did not re-appear after the 3rd or 4th day of sedation.

The baseline values of blood concentrations of propofol obtained just before the infusion was stopped were not statistically different after 24-, 48-, 72- and 96-h infusions at the same rate (fig. 3, table III). By 7.5 min after cessation of infusion,

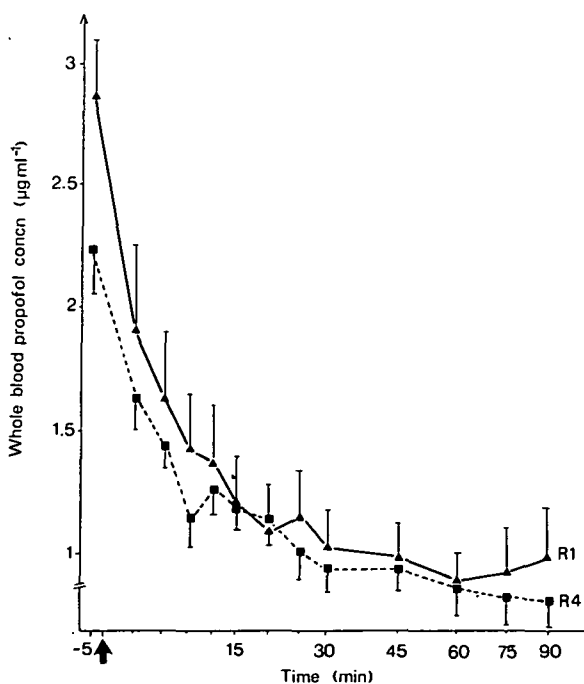


FIG. 3. Decrease in blood propofol concentration (mean (SEM)) following end of infusion (arrow). -5 = Concentration measured 5 min before end of infusion; R1 = changes after the 24-h infusion; R4 = changes after the 96-h infusion. Times on the x-axis are on a log-scale.

the concentrations were less than $1.5 \mu\text{g ml}^{-1}$. The slopes of the decrease in concentration were similar after interruption of the 24-, 48-, 72- and 96-h infusions. A slight secondary peak in drug

concentration occurred at 25 min after the 24-h infusion and at 10 min after the 96-h infusion. However, the magnitudes of these transient increases in drug concentration were not significant.

DISCUSSION

The technique used here differed from those of previous studies in that it was extended over 4 days, it was not initiated by a loading dose of propofol, and it was not accompanied by agents affecting the activity of propofol or modifying neurological status. Our data demonstrate that, in the range $2.75\text{--}3\text{ mg kg}^{-1}\text{ h}^{-1}$ (i.e. at sub-anaesthetic doses), propofol provided adequate sedation for patients undergoing artificial ventilation. Doses for maintenance of general anaesthesia usually exceed $6\text{ mg kg}^{-1}\text{ h}^{-1}$, depending upon the age of the patient and the presence of other agents such as nitrous oxide or fentanyl. The doses used in this study are slightly greater than those of Newman and colleagues [7] ($1.93\text{ mg kg}^{-1}\text{ h}^{-1}$, range $1.03\text{--}2.81\text{ mg kg}^{-1}\text{ h}^{-1}$). In that study, the extent of agitation was less pronounced, and several patients were still under the effect of anaesthetic agents or received additional drugs.

The efficacy of these subanaesthetic infusion rates in our study may be attributed partly to the residual effect of thiopentone $1\text{--}4\text{ mg kg}^{-1}$ given to several patients for intubation, partly to mental and physical exhaustion, and partly to a drug-sparing effect of artificial ventilation. In agitated and restless ICU patients, adequate sedation does not imply deep sleep, but merely control of excessive mental, physical and adrenergic activity.

The level of sedation was controlled easily and recovery was fast, even after a 96-h infusion. The speed of awakening compares favourably with the 12 min required for recovery from Althesin [1]. However, in our study, tracheal intubation was maintained and accurate tests of recovery could not be performed.

The transient resedation occurring in some patients had no clinical significance. It has been observed also with midazolam [9].

The decrease in blood concentrations of propofol was similar to the profile of awakening, changing from the $3\text{-}\mu\text{g ml}^{-1}$ range during sedation to the $1\text{-}\mu\text{g ml}^{-1}$ range at complete recovery. Secondary peaks in blood concentration have been observed also after an induction dose of propofol [10, 11]. These peaks may be the result of changes in cardiac output and regional blood

flow during awakening, leading to the release of propofol from poorly perfused lipid compartments.

The correlation between dose and response on interruption of the infusion at 24 and 96 h suggests that there was neither loss of receptor sensitivity, nor accumulation of drug at receptor sites with increased duration of infusion.

The green- and red-brown colour of urine during infusion of propofol is caused by quinol metabolites of propofol [12]. It is increased by alkalinization and decreased by acidification of urine.

The lack of significant haemodynamic change during 96 h of sedation may be explained by the normal initial circulatory status of our patients, the low dose of propofol used, the provision of a normal fluid balance and the lack of complications.

We have not assessed the effect of propofol on adrenocortical function, but anaesthesia and sedation for 8 h have not been shown to affect cortisol secretion [7, 13, 14].

It is concluded that propofol provides prolonged sedation in ICU patients with rapid control of depth of sedation and without major side effects. The speed of recovery and decrease in blood concentration indicate that propofol does not cumulate under these conditions.

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