



References

- Grant JP. *The State of the World's Children, 1990*. UNICEF. Oxford: Oxford University Press, 1990.
- Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. *Rapport Trimestriel de Statistiques Sanitaires Mondiales* 1992; 45: 180-191.
- Suwanjutha S, Ryangkanchanasetr S, Chantarojanasiri T, Hotrakitya S. Risk factors associated with morbidity and mortality of pneumonia in Thai children under 5 years. *Southeast Asian J Trop Med Public Health* 1994; 25: 60-66.
- Jadavji T, Law B, Lebel MH, Kennedy WA, Gold R, Wang EEL. A practical guide for the diagnosis and treatment of paediatric pneumonia. *CMAJ* 1997; 156: S703-S711.
- Von Schirnding J, Yach D, Klein M. Acute respiratory infections as an important cause of childhood deaths in South Africa. *S Afr Med J* 1991; 80: 79-82.
- Shahir AM, Hon H. Descriptive study on 26 cases of HIV-1 uninfected children with community-acquired pneumonia requiring admission to paediatric ICU (Abstract). *S Afr Med J* 1998; 11: 1458.
- Editorial. Pneumonia in childhood. *Lancet* 1988; 1: 741-743.
- Isaacs D. Problems in determining the etiology of community-acquired childhood pneumonia. *Pediatr Infect Dis J* 1989; 8: 143-148.
- Harris JS. Antimicrobial therapy of pneumonia in infants and children. *Semin Respir Infect* 1996; 11: 139-147.
- Schaad UB. Antibiotic therapy of childhood pneumonia. *Pediatr Pulmonol* 1999; 18: S146-S149.
- Shann F, Germer S, Hazlett D, Gratten M, Linnemann V, Payne R. Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea. *Lancet* 1984; 2: 537-541.
- Shann F. Etiology of pneumonia in children in developing countries. *Pediatr Infect Dis J* 1986; 5: 247-252.
- Adegbola RA, Falade AG, Sam BE, et al. The etiology of pneumonia in malnourished and well-nourished Gambian children. *Pediatr Infect Dis J* 1994; 18: 975-982.
- Korppi M, Heiskanen-Kosma T, Jalonen E, et al. Aetiology of community-acquired pneumonia in children treated in hospital. *Eur J Pediatr* 1993; 152: 24-30.
- Utsunomiya Y, Ahmed K, Rikitomi N, et al. Isolation of pathogenic bacteria from induced sputum from hospitalised children with pneumonia in Bangladesh. *J Trop Pediatr* 1998; 44: 338-342.
- Requyhi HIZ, Guerra MLLS, Dos Santos M, Coccoza AM. Immunodiagnosis of community-acquired pneumonia in childhood. *J Trop Pediatr* 1997; 43: 208-212.
- Leroy O, Sante C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med* 1995; 21: 24-31.
- Wesley AG, Loening WEK. Assessment and 2-year follow-up of some factors associated with severity of respiratory infections in early childhood. *S Afr Med J* 1996; 86: 365-368.
- Richardson DK, Gray JE, McCormick MC, Werkman K, Goldman DA. Score for neonatal acute physiology: A physiologic severity index for neonatal intensive care. *Pediatrics* 1993; 91: 617-623.
- Pollack MM, Ruttiman UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16: 1110-1116.
- Riera-Fanego JF, Wells M, Lipman J, Luyt D, Dance M, Mathiva LR. Demographic and outcome evaluation of a paediatric intensive care unit. *S Afr Med J* 1997; 87: 1586-1590.
- Vardas E, Blaauw D, McAnerney J. The epidemiology of respiratory syncytial virus (RSV) infections in South African children. *S Afr Med J* 1999; 89: 1079-1084.
- Baker KA, Ryan ER. RSV infection in infants and young children. *Postgrad Med* 1999; 106: 97-109.
- Feldman C, Ross S, Mahomed AG, Omar J, Smith C. The aetiology of severe community-acquired pneumonia and its impact on initial empiric, antimicrobial chemotherapy. *Respir Med* 1995; 89: 187-192.
- Gratten M. Laboratory guidelines for blood cultures in Papua New Guinea. *P N G Med J* 1983; 26: 222-227.
- Schindler MB, Cox PN. A simple method of bronchoalveolar lavage. *Anaesth Intens Care* 1994; 22: 66-68.
- Pugin J, Auckenthaler R, Mili N, Janssens J, Lew PD, Suter PM. Diagnosis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991; 143: 1121-1129.
- Gaussorgues P, Piperno D, Bachmann P, et al. Comparison of nonbronchoscopic bronchoalveolar lavage to open lung biopsy for the bacteriologic diagnosis of pulmonary infections in mechanically ventilated patients. *Intensive Care Med* 1989; 15: 94-98.

EFFECT OF 1% AND 2% PROPOFOL ON BLOOD LIPIDS DURING LONG-TERM SEDATION

André Coetzee, Edward M Blaine, D Labadarios, Robert Schall, Matthias Haus

Objectives. To compare the effects of 1% and 2% propofol on the maximum and average lipid levels, the relative frequency of hyperlipidaemia, the propofol dose required to achieve an equivalent degree of sedation, the pharmacodynamic effects at the required infusion rates, and the effect on respiratory function.

Design. Open, randomised, parallel group, multicentre comparison study.

Setting. Intensive care units (ICUs) at the Faculty of Medicine, University of Stellenbosch and at Vergelegen Medicity, Somerset West.

Subjects. Patients who were artificially ventilated for at least 72 hours in the ICUs and who required sedation or analgesia.

Outcome measures. Continuous intravenous infusion of 1% or 2% propofol to provide an administration rate in the range of 1 - 4 mg/kg/h. The initial infusion rate was about 2 mg/kg/h, adjusted to achieve the appropriate level of sedation.

Results and conclusions. Seventy-five patients were enrolled in the study, of which 72 were evaluable for safety analysis and 58 were evaluable for efficacy analysis. The total daily dose of propofol (ml/day) in the 2% propofol group was about 60% of that in the 1% propofol group, indicating that the lipid load in the 2% propofol group had only slightly more than half the lipid load in the 1% propofol group. Thirteen of 27 patients (48%) in the 2% propofol group had abnormally

Department of Anaesthesiology and Critical Care, University of Stellenbosch, Tygerberg, W Cape

André Coetzee, MB ChB, PhD, MMed (Anaes), FFA (SA), FFARCS, MD, PhD

Vergelegen Medicity, Somerset West

Edward M Blaine, MB ChB, FFA (SA)

Department of Human Nutrition, University of Stellenbosch, Tygerberg, W Cape

D Labadarios, BSc(Hons), MB ChB, PhD, FACN

Quintiles ClinData, Bloemfontein

Robert Schall, PhD

AstraZeneca Pharmaceuticals, Private Bag X7, Gallo Manor

Matthias Haus, MB ChB, MD, DCH (SA), MFGP (SA), Dip Mid COG (SA), FFFPM



high triglyceride levels compared with 19 of 31 patients (61%) in the 1% propofol group. Similarly, 1 of 22 patients (4%) in the 2% propofol group had lipaemia compared with 4 of 30 patients (13%) in the 1% propofol group. Abnormal cholesterol levels, alveolar-arterial oxygen tension gradient and daily percentage of time with desired sedation were comparable between the two groups. The observed incidence of raised plasma triglyceride concentrations, and of lipaemia, was lower in the 2% propofol group than in the 1% propofol group, although the differences were not statistically significant. The 2% formulation of propofol appears to be as effective and at least as safe as 1% propofol.

S Afr Med J 2002; 92: 911-916

The 1% formulation of propofol (Diprivan, AstraZeneca) is used widely for induction and maintenance of anaesthesia and in some countries for sedation of adult patients receiving intensive care. To reduce the amount of lipid administered in association with propofol, a 2% formulation of propofol has been developed. This formulation contains 20 mg/ml propofol and an unchanged amount of soybean oil (10%). Therefore for any given dose of propofol the lipid load is reduced by 50% when compared with the 1% solution.

In four clinical studies which compared the 2% propofol formulation with the standard 1% formulation, pharmacodynamic equivalence and similar pharmacokinetic parameters were demonstrated and no significant differences in the safety profiles of the two preparations were encountered.¹⁻⁴ In one of the studies,⁴ however, a significantly greater increase in plasma triglyceride concentration was observed in patients given 1% propofol. In another study⁵ in which plasma triglyceride concentration was measured, no difference was observed. This may have been due to the relatively low total lipid load administered in this study.

Some publications^{6,7} have suggested that the prolonged infusion of 1% propofol may be associated with increased dose requirements to maintain the desired level of sedation in intensive care. In some cases this has been associated with hypertriglyceridaemia.

Greene *et al.*⁸ investigated the effect of Intralipid-induced hyperlipidaemia on pulmonary function and concluded that the minor changes observed were unlikely to be of any clinical consequence in patients without any pre-existing pulmonary or pulmonary vascular disease. While no consistent effect on pulmonary function was observed in the studies that included 2% propofol, there was a trend at some time points suggesting a reduction in alveolar-arterial oxygen gradient.

The principal objectives of this study, therefore, were to compare 1% and 2% propofol with regard to maximum and

average lipid (triglyceride and cholesterol) levels and the relative frequency of hyperlipidaemia (i.e. an increase in serum triglyceride level above the upper limit of the normal range), the propofol dose required to achieve an equivalent degree of sedation, and the effect on respiratory function, and in particular arterial oxygenation.

METHODS

Study population

Patients of either sex, at least 18 years old, who were artificially ventilated for at least 72 hours in the ICUs and who required sedation or analgesia, were enrolled in this study. Exclusion criteria included allergy to the trial drugs, previous adverse experience of general anaesthesia or sedation, pregnancy, head injury or coma, use of neuromuscular blocking drugs other than short-acting agents required to facilitate the insertion of an endotracheal tube, disorders of lipid metabolism, and the use of intravenous lipids other than propofol.

Informed consent was given by the patient or next of kin. Approval from the relevant ethics committees was obtained for the study.

Study design

This was an open, randomised, parallel group, multicentre (two-centre) comparison of 1% and 2% propofol. The intended duration of therapy with propofol was at least 72 hours. When necessary, patients in both groups were treated with an infusion of morphine 1 - 2 mg/h, started at the same time as the infusion of propofol. The study treatments were: (i) 1% propofol 2 mg/kg/h; and (ii) 2% propofol 2 mg/kg/h.

Patients were sedated with a continuous intravenous infusion of 1% or 2% propofol to provide an administration rate in the range of 1 - 4 mg/kg/h. The initial infusion rate was about 2 mg/kg/h; thereafter it was adjusted to achieve the appropriate level of sedation. Wherever possible, sedation was initiated with an infusion of propofol. All patients were ventilated with oxygen-enriched air to maintain arterial carbon dioxide tension (P_{aCO_2}) at 4.0 - 5.5 kPa. The infusion of propofol was discontinued when the patient was to be weaned from the ventilator.

Concomitant medication such as antibiotics, inotropic agents and intravenous fluids were given to the patients as required. Lipid emulsion-free total parenteral nutrition was administered to these patients who met the criteria for nutrition support.

Efficacy assessment

For each study day, the total volume of propofol used was recorded. The total duration and daily dose of propofol were recorded, and the daily infusion rate (mg/kg/h) was calculated in the analysis. The dose of morphine used (mg) was



calculated in the same way. The level of sedation was assessed daily using a modification of the scale proposed by Ramsay *et al.*⁹

A baseline venous blood sample was collected before the initiation of the propofol sedation, for measurement of plasma triglyceride and cholesterol concentration. Thereafter, venous blood samples were taken at the same time each day during the period of propofol administration and 24 hours following the last dose of propofol. The presence of any lipaemia on visual inspection of plasma samples was noted.

Statistical analysis

The two treatment groups were compared with regard to the following variables:

1. Primary criteria: (i) maximum and average lipid concentration for the time period on propofol treatment (infusion); (ii) relative frequency of hypertriglyceridaemia (occurrence of abnormal lipid levels, presence of lipaemia ascertained by visual inspection) — the normal range for triglyceride was 0.9 mmol/l - 1.97 mmol/l and for cholesterol 3.8 mmol/l - 5.7 mmol/l; (iii) propofol dose rates; and (iv) alveolar-arterial oxygen tension gradient for each day during propofol infusion.

2. Secondary criteria: (i) percentage of time with adequate sedation; and (ii) overall assessment of sedation.

The two treatment groups were compared with regard to maximum and average plasma lipid concentration (triglyceride and cholesterol), dose rates, and the alveolar-arterial oxygen tension gradient by calculating estimates and 95% confidence intervals (CIs) for the true 2% propofol/1% propofol mean ratios in these variables. Estimates and CIs for the mean ratios were calculated by taking the antilog of the conventional point estimates and confidence limits for mean differences obtained from an analysis of variance (ANOVA) of the log-transformed data with treatment and centre as main effects. The two treatment groups were also compared with respect to the proportion of patients with abnormal lipid levels, and with regard to the proportion of patients with lipaemia, by calculating estimates and 95% CIs for the true 2% propofol - 1% propofol difference in those proportions between the treatment groups.¹⁰

RESULTS

Data sets analysed

Seventy-five patients were enrolled in the study, of which 72 received treatment. All patients who received treatment were evaluable for safety analysis and 58 patients were evaluable for efficacy analysis. Seventeen patients were excluded from the efficacy analysis for the following reasons: violation of entry criteria ($N = 1$), did not receive propofol ($N = 3$), protocol violations ($N = 2$), less than 72 hours of propofol treatment

Table I. Demographic data (efficacy population)

	1% propofol ($N = 31$)		2% propofol ($N = 27$)	
	Male	Female	Male	Female
No. of patients	14	17	18	9
Age (yrs)				
Mean	48.5	43.8	50.3	44.3
Range	21.6 - 71.0	19.9 - 76.1	22.6 - 71.0	19.5 - 76.4
Weight (kg)				
Mean	75.1	66.6	73.8	62.3
Range	58.2 - 110	55.0 - 90.0	55.0 - 92.0	50.0 - 90.0
Apache II score				
Median	14	11	14.5	9.5
Range	3 - 22	3 - 27	3 - 26	2 - 22

($N = 8$), and raised triglyceride levels before propofol infusion ($N = 3$). The demographic data of the patients evaluable for efficacy analysis are summarised in Table I.

Adverse events

Raised triglyceride levels were the most frequently reported adverse event, occurring in 10 out of 37 patients (27%) in the 1% propofol group and 4 out of 35 patients (11%) in the 2% propofol group.

Deaths

One patient died as a result of trauma before starting treatment with propofol. Six patients died after start of the propofol infusion: 2 patients had cardiac arrest (1 patient in each group, definitely not related to propofol); 1 patient had pulmonary oedema with underlying tuberculosis (2% propofol group, probably not related to propofol); 1 patient was hyperglycaemic on admission (2% propofol group, definitely not related to propofol); 1 patient died after a hypertensive episode with ventricular arrhythmias and asystole (2% propofol group, probably not related to propofol); 1 patient died from multiple organ failure (1% propofol group, probably not related to propofol).

Lipid levels

Fewer patients in the 2% propofol group had abnormally raised plasma triglyceride concentrations compared with the 1% propofol group. Abnormal cholesterol levels occurred with similar frequency in the two groups, but fewer patients in the 2% propofol group had lipaemia than in the 1% propofol group (Table II).

The observed maximum and average concentrations of plasma triglyceride and cholesterol were lower in the 2% propofol group compared with the 1% propofol group,



Table II. Number and proportion of patients with abnormal plasma lipid levels* (efficacy population)

	1% propofol	2% propofol	Difference [†]	95% CI [‡]
Abnormal triglyceride (%)	19/31 (61)	13/27 (48)	-13	-39 - 12
Abnormal cholesterol [§]	3/31 (10)	3/27 (12)	1	-14 - 17
Lipaemia (%)	4/30 (13)	1/27 (4)	-9	-23 - 5

* Triglyceride levels above normal range, cholesterol levels below normal range or visible lipaemia, any time during propofol treatment; normal range for triglyceride was 0.9 mmol/l - 1.97 mmol/l and for cholesterol 3.8 mmol/l - 5.7 mmol/l.

† 2% propofol - 1% propofol difference of proportions.

‡ 95% confidence interval (CI) for the 2% propofol - 1% propofol difference of proportions.

§ All abnormal cholesterol levels were below normal.

although the corresponding CI for the 2% propofol/1% propofol mean ratios were wide and included 100%, so that a statistically significant difference could not be shown (Table III).

Alveolar-arterial oxygen tension gradient

The two treatments were similar with regard to the alveolar-arterial oxygen tension gradient (Table IV).

Propofol and morphine infusion times and doses

The mean values and ranges of the dose rates of propofol and morphine are summarised in Table V. The average daily dose of propofol (ml/day) in the 2% propofol group was about 60% of that in the 1% propofol group, indicating that the 2% propofol group had only slightly more than half the lipid load

Table V. Mean values (ranges) of propofol and morphine infusion time and doses (efficacy population)

	1% propofol (N = 31)	2% propofol (N = 27)
Total duration of propofol (h)	125 (28 - 262)	119 (68 - 231)
Total dose of propofol (ml)	1 775 (350 - 3 946)	1 039 (205 - 1 910)
Daily dose of propofol (ml/day)	360 (121 - 838)	219 (70.3 - 509)
Total duration of morphine (h)	86.2 (0 - 268)	81.3 (0 - 174)
Total dose of morphine (mg)	221 (0 - 1 157)	153 (0 - 368)
Average % desired sedation	92.9 (40 - 100)	91.9 (66 - 100)

Table III. Maximum and average concentration (mmol/l) of plasma triglycerides and cholesterol (efficacy population)

	1% propofol				2% propofol				Mean ratio	
	N	Geometric mean	SD	Range	N	Geometric mean	SD	Range	(%) [†]	95% CI (%) [‡]
Triglycerides										
C _{max}	31	2.32	1.58	0.80 - 5.47	27	2.02	1.61	0.84 - 6.52	87	68 - 111
C _{av}	31	1.58	1.47	0.63 - 3.22	27	1.37	1.56	0.59 - 3.91	87	70 - 108
Cholesterol										
C _{max}	31	3.72	1.39	2.13 - 6.10	27	3.25	1.51	1.14 - 6.44	87	72 - 106
C _{av}	31	2.85	1.44	1.34 - 4.99	27	2.48	1.48	0.88 - 5.35	87	71 - 106

* Point estimate for 2% propofol/1% propofol mean ratio from analysis of variance with treatment and centre as main effects.

† 95% confidence interval (CI) for the 2% propofol/1% propofol mean ratio from analysis of variance with treatment and centre as main effects.

SD = standard deviation; C_{max} = maximum concentration; C_{av} = average concentration.

Table IV. Alveolar-arterial oxygen tension gradient (efficacy population)

	1% propofol				2% propofol				Mean ratio (%) [*]	95% CI (%) [†]
	N	Geometric mean	SD	Range	N	Geometric mean	SD	Range		
Day 1	30	266	1.57	130 - 637	26	223	1.46	81.0 - 611	84	67 - 105
Day 2	30	223	1.43	136 - 667	26	230	1.31	151 - 429	103	87 - 103
Day 3	27	221	1.49	112 - 570	26	225	1.37	109 - 400	102	84 - 124
Day 4	28	218	1.52	104 - 604	26	220	1.46	92.1 - 464	101	81 - 126
Day 5	26	205	1.44	120 - 551	21	226	1.46	107 - 568	110	88 - 136

* Point estimate for 2% propofol/1% propofol mean ratio from analysis of variance with treatment and centre as main effects.

† 95% confidence interval (CI) for the 2% propofol/1% propofol mean ratio from analysis of variance with treatment and centre as main effects.



of the 1% propofol group. The total dose of morphine in the 2% propofol group is about 30% lower than in the 1% propofol group.

Sedation

The treatment groups are similar with regard to the daily percentage of time with desired sedation (Table V). Twenty-two of 30 patients (73%) in the 1% propofol group and 21 of 26 patients (81%) in the 2% propofol group had a good quality of sedation. Similarly, 21 of 30 patients (70%) in the 1% propofol group and 19 of 26 patients (73%) in the 2% propofol group had good control of sedation (Table VI).

Table VI. Overall quality and control of sedation (efficacy population)

	1% propofol	2% propofol	Difference* (%)	95% CI (%) ^b
Quality				
Good (%)	22/30 (73)	21/26 (81)	7	-15 - 29
Adequate (%)	8/30 (27)	4/26 (15)		
Poor (%)	0/30 (0)	1/26 (4)		
Control				
Good (%)	21/30 (70)	19/26 (73)	3	-21 - 27
Adequate (%)	9/30 (30)	7/26 (27)		
Poor (%)	0/30 (0)	0/26 (0)		

* 2% propofol - 1% propofol difference of proportions.
[†] 95% confidence interval (CI) for the 2% propofol - 1% propofol difference of proportions.

DISCUSSION

Propofol has a suitable pharmacokinetic profile for use in the ICU and a number of studies have indeed confirmed that propofol offers good quality sedation, is easily adjustable and has a short wake-up time when used as an intravenous agent in intensive care.¹¹⁻¹⁷ Our results support those published previously inasmuch as we found propofol easy to use and with few or no serious side-effects. In addition, we could not demonstrate any difference in either the management of the infusion regimen, or in the incidence of side-effects when we compared the 1% with the 2% propofol solution.

There has been concern about the effects of intravenous lipids on pulmonary and pancreatic function. A number of studies evaluated the effect of 1% and 2% propofol on serum triglycerides, cholesterol and pulmonary function. Gottardis and colleagues¹⁸ could not show any change in serum lipid

levels in non-septic patients during the 1% propofol administration. Eddleston and Shelley,¹⁹ however, reported a significant increase in triglyceride and cholesterol levels in a single patient who received prolonged propofol sedation. The 2% propofol solution was used for intensive care sedation and this did not result in demonstrative pulmonary dysfunction in either the 1% or 2% propofol group.²⁰

The concern about the effect of raised serum triglycerides on pulmonary function was extrapolated from the fat embolism syndrome and it was speculated that lipids given intravenously impair lung function and gas exchange.²¹ However, clinical studies have revealed a less clear picture: following a 0.24 g/kg/h dose (for 16 hours) of intravenous lipids, Van Deyk *et al.*²² could not demonstrate any change in pulmonary artery pressure and the shunt fraction in patients suffering from acute respiratory distress syndrome (ARDS) and sepsis who received intravenous lipids.²³ In addition, the pulmonary artery wedge pressure increased while the systemic vascular resistance decreased after the administration of lipids.²³

The mechanism for the alteration in pulmonary function and pulmonary haemodynamics is not clear. Early studies suggested impaired diffusion associated with a raised serum triglyceride level.²³ More recent data indicate that altered prostaglandin production could explain the observed changes in pulmonary function. McKeen *et al.*²⁴ demonstrated a decreased arterial oxygen tension and increased pulmonary artery pressure during 10% Intralipid infusion (0.25 g/kg/h), which could be blocked with indometacin (but not heparin) administration. It has been speculated that intravenous lipids increase the vasodilatory prostanoids resulting in ventilation-perfusion mismatch in the lung.²⁴⁻²⁶ However, no cause-and-effect relationship (for lipids, prostaglandins and altered pulmonary function) has been demonstrated in human studies.²⁷ The effect of lipids on pulmonary function is small and is unlikely to have clinical consequences.^{25, 28}

In our study we used the AaDO₂ to evaluate pulmonary function. However, one needs to interpret the AaDO₂ carefully as it has been demonstrated that this index is influenced by the inspired oxygen fraction.²⁹ In addition, poor correlation was found between the Qs/Qt and AaDO₂ and it was speculated that the mixed venous oxygen saturation has a significant effect on the AaDO₂.²⁹ However, despite this criticism, it can be stated that in this study the infusion of either 1% or 2% propofol did not appear to have any influence on the clinician's ability to oxygenate the patients.

Hypertriglyceridaemia has been reported to predispose to pancreatitis.^{30, 31} Triglyceride levels in excess of 11.3 mmol/l increase the likelihood of pancreatitis and although there is an association between alcohol ingestion, triglycerides and pancreatitis, it does appear that raised triglycerides *per se* can cause pancreatitis.³⁰



Because of the potential detrimental effect of raised serum triglycerides on patients, we screened patients for raised triglycerides before commencing the propofol infusion. This may have introduced bias inasmuch as we excluded a group that was at risk for developing further raised lipid levels. However, it was not thought to be acceptable ethically to subject patients, who already have raised triglycerides, to a further risk and hence this exclusion criterion was deemed necessary.

In this study the total daily dose of propofol (ml/day) in the 2% propofol group was about 60% of that in the 1% propofol group, indicating that the lipid load in the 2% propofol group was slightly higher than half the lipid load in the 1% propofol group. The observed incidence of raised triglyceride levels and of lipaemia was lower in the 2% propofol group than in the 1% propofol group. However, because of the relatively small sample size no definite conclusion in favour of the 2% propofol treatment can be made. It does, however, appear that the 2% propofol solution is as safe as the 1% solution in this respect. Furthermore, it does not seem that propofol, as used in this trial, interferes with pulmonary function of critically ill patients and whatever changes there may have been were comparable between the two groups. Nevertheless, the use of the more concentrated 2% propofol solution would imply that a smaller load of lipid emulsion would have to be administered to the patient. This may hold distinct advantages for the patient in view of the recently reported increased susceptibility to infection and decreased T-cell function in trauma patients receiving lipid infusions (25% of non-protein energy) as part of total parenteral nutrition.³²

We conclude that the results of this comparative trial indicate that the efficacy and safety of the two treatments are similar.

This study was financially supported by AstraZeneca Pharmaceuticals.

References

1. Dewandre J, Van Bos R, Van Hemelrijck J, Van Aken H. A comparison of the 2% and 1% formulations of propofol during anaesthesia for craniotomy. *Anaesthesia* 1994; **49** (1): 8-12.
2. Montanini S, Pratico C, Leone D, et al. Comparison between 1% and 2% formulations of propofol during sedation in intensive care (Italian). *Minerva Anestesiol* 1995; **61**: Suppl 1; 85-88.
3. Servin FS, Desmots JM, Melloni C, Martinelli G. A comparison of 2% and 1% formulations of propofol for the induction and maintenance of anaesthesia in surgery of moderate duration. *Anaesthesia* 1997; **52**: 1216-1221.
4. Van Bos R, Van Hemelrijck J, Hulsey B, Van Aken H. Comparison between 1 and 2% propofol emulsion in neurosurgical patients. *Anesth Analg* 1992; **74**(25) Feb Abstract 5329. 66th Congress of the International Anesthesia Research Society, San Francisco, 13-17 March 1992.
5. Ewart MC, Yau KW, Morgan M. Comparison of 1% and 2% formulations of propofol for sedation following cardiac surgery. *J Drug Dev* 1991; **4**: Suppl 3: 59-61.
6. Foster SJ, Buckley PM. A retrospective review of two years experience with propofol in one intensive care unit. *J Drug Dev* 1989; **2**: 73-74.
7. Boyle WA, Shear JM, White PE, et al. Tolerance and hyperlipemia during long-term sedation with propofol. *Anesthesiology* 1990; **73**: A245.
8. Greene HL, Hazlett D, Demaree R. Relationship between intra-lipid induced hyperlipemia and pulmonary function. *Am J Clin Nutr* 1976; **29**: 127-135.
9. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974; **2**: 656-659.
10. Gardner MJ, Altman DG. *Statistics with Confidence — Confidence Intervals and Statistical Guidelines*. 1st ed. London: British Medical Journal, 1989.
11. Cockshott ID, Douglas EJ, Prys-Roberts C, Turtle M, Coates DP. The pharmacokinetics of propofol during and after intravenous infusion in man. *Eur J Anaesthesiol* 1990; **7**: 265-275.
12. Harris CE, Grounds RM, Murray AM, Lumley J, Royston D, Morgan M. Propofol for long-term sedation in the intensive care unit. *Anaesthesia* 1990; **45**: 366-372.
13. Newman LH, McDonald JC, Wallace PGM, Ledingham I McA. Propofol infusion for sedation in intensive care. *Anaesthesia* 1987; **42**: 929-937.
14. Beller JP, Pottecher T, Lugnier A, Mangin P, Otteni JC. Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion. *Br J Anaesth* 1988; **61**: 583-588.
15. Grounds RM, Lalor JM, Lumley J, Royston D, Morgan M. Propofol infusion for sedation in the intensive care unit: preliminary report. *BMJ* 1987; **294**: 397-400.
16. Roekaerts PM, Huygen FJ, De Lange S. Infusion of propofol vs. midazolam for sedation in the intensive care unit following coronary artery surgery. *J Cardiothorac Vasc Anesth* 1993; **7**: 142-147.
17. Boyd O, Mackay CJ, Rushmer F, Bennette D, Grounds RM. Propofol or midazolam for short-term alterations in sedation. *Can J Anaesth* 1993; **40**: 1142-1147.
18. Gottardis M, Kühnl-Brady KS, Koller W, Sigl G, Hackl JM. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. *Br J Anaesth* 1989; **62**: 393-396.
19. Eddleston JM, Shelley MP. The effect on serum lipid concentrations of a prolonged infusion of propofol-hypertriglyceridaemia associated with propofol administration. *Intensive Care Med* 1991; **17**: 424-426.
20. Ewart MC, Yau KW, Morgan M. 2% Propofol for sedation in the intensive care unit. A feasibility study. *Anaesthesia* 1992; **47**: 146-148.
21. Nixon JR, Broch-Utne JG. Free fatty acid and arterial oxygen changes following major injury: a correlation between hypoxemia and increased free fatty acid levels. *J Trauma* 1978; **18**: 23-26.
22. Van Deyk K, Hempel V, Münch F, Kopp M, Graf H, Epple E. Influence of parental fat administration on the pulmonary vascular system in man. *Intensive Care Med* 1983; **9**: 73-77.
23. Venus B, Smith RA, Patel C, Sandoval E. Hemodynamic and gas exchange alterations during intralipid infusion in patients with ARDS. *Chest* 1989; **95**: 1278-1281.
24. McKeen CR, Brigham KL, Bowers RE, Harris TR. Pulmonary vascular effects of fat emulsion infusion in unanesthetized sheep. Prevention by indomethacin. *J Clin Invest* 1978; **61**: 1291-1297.
25. Inwood RJ, Gora P, Hunt CE. Indomethacin inhibition of intralipid-induced lung dysfunctions. *Prostaglandins Med* 1981; **6**: 503-514.
26. Hageman JR, McCulloch K, Gora P, Olsen EK, Pachman L, Hunt CE. Intralipid alterations in pulmonary prostaglandin metabolism and gas exchange. *Crit Care Med* 1983; **11**: 794-798.
27. Mathru M, Dries DJ, Zecca A, Fareed J, Rooney MW, Rao TL. Effect of fast vs slow intralipid infusion on gas exchange, pulmonary hemodynamics, and prostaglandin metabolism. *Chest* 1991; **99**: 426-429.
28. Greene HL, Hazlett D, Demaree R. Relationship between intralipid-induced hyperlipemia and pulmonary function. *Am J Clin Nutr* 1976; **6**: 503-514.
29. Coetzee A, Swanevelder J, van der Spuy G, Jansen J. Gas exchange indices — how valid are they? *S Afr Med J* 1995; **85**: 1227-1232.
30. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am* 1990; **19**: 783-791.
31. Steinberg W, Tenner S. Acute pancreatitis. *N Engl J Med* 1994; **330**: 1198-1210.
32. Battistella FD, Widegren JT, Anderson JT, Siepler JK, Weber JC, MacColl K. A prospective, randomised trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma* 1997; **43**: 52-58.

Accepted 25 March 2002.