Title : PHARMACOKINETICS OF PROPOFOL ADMINISTRATED BY PROLONGED CONTINUOUS INTRAVENOUS INFUSION IN MAN.

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Introduction. Patients in intensive care unit and under prolonged controlled mechanical ventilation may require a sedation. Rapid reversibility of the sedation may be needed to assess neurological status of patients. Thus it is valuable to use a drug whose distribution and metabolism result in a short plasma half-life. Propofol is a short acting hypnotic drug whose pharmacokinetics make it suitable for use by continuous intravenous administration.

Patients and methods. After institutional approval, this study included 6 patients, 4 males, 2 females with a mean age of 50 ± 23 years (mean ± SD). These patients were free from previous hepatic disease and were under controlled mechanical ventilation for neurologic disease in 4 cases (2 post-ischemic brain damages, 1 head trauma, 1 meningo-encephalitis) and for acute respiratory insufficiency in 2 cases. They received a FiO^2 between 0.3 and 0.5 and tidal volume and respiratory rate were adjusted to maintain blood gas levels within normal range. Propofol was first given as a bolus induction dose of 1 to 3 mg/kg intravenously within 1 min. Then propofol was given at a constant flow rate at a dose of 3 mg/kg/h for 3 days through a central venous line. Blood samples were taken from a radial artery catheter inserted in the non-dominant arm. Samples were obtained before and 1 min. after the bolus injection and then 1 min., 10 min., 20 min., 40 min., 60 min., 2 h, 4h, 6h and every 12 h during infusion. After the infusion was stopped, arterial blood samples were obtained 5 min., 10 min., 40 min., 1h, 2h, 4h, 6h, 12h and every 12h until the 5th day. Samples were placed in tubes containing potassium oxalate, mixed throughly and then stored at 4°C before analysis. Whole blood propofol concentrations were measured following extraction into cyclohexane by a high pressure liquid chromatographic method using fluorescence detection. For all patients, elimination half-life was calculated by the classical least square method and clearance was assessed according to the relationship : Cl = Dose/AUC. In 4 patients, plasma concentrations were fitted to bi and tri compartimental model and individual parameters were estimated using the maximum likelihood estimation procedure (APIS program).

Results. Propofol concentrations plotted against time are given in figure 1. After bolus injection there was a decrease in concentration and the minimum level (1174 ± 522 ng/ml) was reached at the 4th hour. A steady state was obtained at the 18th hour, the maximum level being 2009 ± 835 ng/ml. After the infusion was stopped, there was a secondary peak in the drug concentration between the 1st and 2nd hour and then concentrations declined in a curvilinear manner. Kinetic analysis was performed using bi or tricompartimental model. Results are given in table 1.

Discussion. When propofol is administered by prolonged continuous intravenous infusion, pharmacokinetic parameters are not similar to those observed after single bolus dose, or short term infusion (1, 2) : plasma elimination half-life and Vd area are dramatically increased and only total body clearance is unchanged. This might be explained by a storage in a poorly perfused deep compartment (probably fat) with a slow return of propofol into blood.

References.

1. Cockshott ID : Propofol pharmacokinetics and metabolism - an overview. Postgrad. Med. J. 61, (suppl. 3) : 45-50, 1985.
2. Gepts E., Claeys A.M., Camu F. : Pharmacokinetics of propofol administered by continuous intravenous infusion in man. A preliminary report. Postgrad. Med. J. 61, (suppl. 3) : 51-52, 1985.

Trialist	Present study	GEPTS and al. (2)	COCKSHOTT (1)
T 1/2(h)	28,4 ± 11	3,7 ± 0,3	6,4 - 8,3
Vd_{area} (l)	1632 ± 670	517,19 ± 139	387 -1587
Cl_{tot} ($l.min^{-1}$)	1,8 ± 0,84	1,6 ± 0,85	1,91 - 2,2
V_i (l)	37 ± 15	-	22 - 67

Vi = volume of central compartment ; Vd_{area} = apparent volume of distribution ; Cl_{tot} : total body clearance ; T1/2 = terminal elimination half-life.

TABLE I :

Pharmacokinetics of propofol

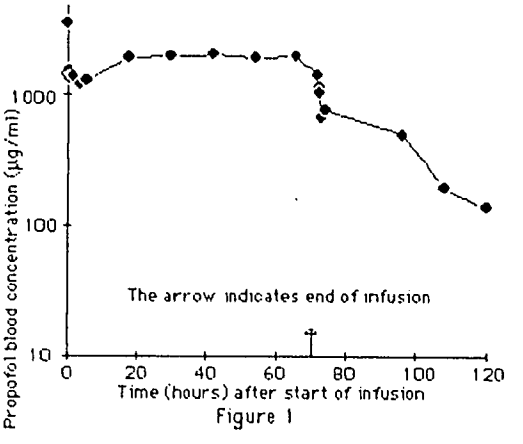

Figure 1