A312

TITLE: RATE OF INFUSION OF PROPOFOL FOR CONSTANT CONCENTRATION DIFFERS FROM PHARMACOKINETIC PREDICTION

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We have used the Plasma Drug Efflux, error correcting method[1], to determine the average variable rate infusion profile necessary to maintain a constant arterial blood concentration of propofol when used as the primary anaesthetic during surgery.

With institutional approval and informed consent we administered continuous infusions of propofol to adult patients coming to major head and neck surgery or neurosurgery, using a specially constructed programmable infusion pump.

The first patient was dosed according to her lean body mass (LBM), calculated from weight and height, with a fixed rate infusion of 0.06 mg $min^{-1}kgLBM^{-1}$. Arterial blood concentrations were later measured by HPLC and the result divided into the infusion rate at each time. Resulting data (ml $min^{-1}kgLBM^{-1}$) was used to infuse a further two patients for a target concentration (C_T) of 3 μg ml^{-1} (See[1]). The process was repeated for two more groups of patients.

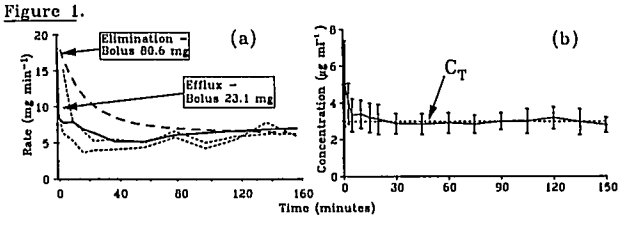
Figure 1(a) shows the infusion rates used in the second and third groups (thin broken lines) and the bolus and infusion rate used to infuse the final group of patients ("Efflux"-solid line) Also in Figure 1(a) is the prediction for initial dose and infusion rate from single dose pharmacokinetic data ("Elimination -heavy broken line) derived from a three compartment model[2] by conventional methods[3]. Each of the infusion rate profiles shown in Figure 1(a) are scaled to the rate predicted to establish and maintain a concentration of 3 μg ml^{-1} in a 70 kg subject with 20% body fat.

Figure 1(b) shows the mean (±SD) of arterial concentrations of propofol in the fourth group of subjects (n=12) shown against the C_T (broken line). These concentrations have a small bias from C_T over the full infusion period of 150 min.

During the first hour the infusion rate was considerably less than predicted from pharmacokinetic data. The lower infusion rate, which returns to the predicted rate later, might be explained by transient depressant effects of propofol on the cardiovascular system.

References: 1. Anesthesiology 67:32-41, 1987.
2. British J Anaesthesia 60:146-150, 1988.
3. Europ J Clinical Pharmacol 28:543-552.1985.

Figure 1.



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TITLE: COMPUTER-CONTROLLED PROPOFOL INFUSION: COMPARISON OF THREE PHARMACOKINETIC MODELS.

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The pharmacokinetic properties of propofol (P) make it particularly suitable for continuous infusion. During infusion, a computer is able to make real-time estimations of P concentrations, however this requires the a-priori choice of a pharmacokinetic model (PM). The aim of this study was to compare the accuracy of 3 three-compartment PM described in the literature: Gepts(G), Kirpatrick(old patients) (KO) and Kirpatrick(young patients) (KY)(1, 2).

Methods: 10 patients, 6 men, 4 women (mean age: 52±14, range: 33-72 years, mean weight: 61±16, range: 47-86 kg), scheduled for a colonoscopy, were included after institutional approval and informed consent. A computer (Macintosh°)controlled an Ivac 560° volumetric infusion pump and made the real-time estimations of P theorical concentrations. Patients were not premedicated. During anaesthesia, the patients spontaneously breathed an oxygen-air mixture. The infusion scheme was 20 mg.kg-1 for 5 min followed by 9 mg.kg-1 for 30 min and finally 6 mg.kg-1 until 50th min. When analgesia was not sufficient, a 7 μg.kg-1 bolus of alfentanyl was injected. Venous blood samples were taken before and 4.5, 10, 34 and 50 min after the beginning of infusion. Real P concentrations were measured by HPLC. The accuracy of the 3 PM was evaluated following the principles suggested by Sheiner (3): absolute bias (B) (μg.ml-1) and absolute precision (Pr) (μg2.ml-1).

Results: B and its confidence interval and Pr for the 3 PM are shown in table I. Table II compares the Pr of the 3 PM.

Conclusions: in this study, the most accurate PM appeared to be G: there was B and it had the highest Pr. This could be explained by the fact that this PM was established using a P infusion scheme; conversely, the K models were estimated after a P bolus injection. New methods, which can calculate individual pharmacokinetic parameters, should improve the performance of P computer-controlled infusion in anaesthesia.

Models	B	IC (B)	Pr
G	-0.01	-0.73;0.27	0.27
KO	1.07	0.39;1.39	1.76
KY	0.93	0.25;1.25	1.34

TableI: accuracy of the 3 PM

Models	Pr1-Pr2	IC(Pr1-Pr2)
G vs KO	-1.06	-1.27;-0.27
G vs KY	-0.65	-1.00;-0.01
KO vs KY	0.41	-0.53; 1.52

Table II:comparison of the 3 Pr

References: 1 - E Gepts, F Camu, ID Cockshott. Anesth Analg, 1987, 66, 1256-63 2 - T Kirpatrick, ID Cockshott, EJ Douglas. Br J Anaesth, 1988, 60, 146-150 3 - LB Sheiner, SL Beal. J Pharmacokinet Biopharm, 1981, 9, 503-12.