PLASMA CONCENTRATIONS OF DOXAPRAM IN MAN DURING VARIABLE-RATE INTRAVENOUS INFUSION

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Doxapram is used as a respiratory stimulant in patients with respiratory failure and in post-operative patients; pharmacokinetic properties in man have recently been investigated (Robson & Prescott, 1979). In this study we report results obtained with a variable-rate intravenous infusion regimen; this was designed to achieve rapidly and maintain a constant plasma doxapram concentration during studies on respiratory function in healthy volunteers over a 1-h period. Subsequently the regimen was tried in a bronchitic patient over 4h.

Six fasting volunteers received an intravenous injection of doxapram (1.5 mg kg^{-1}) and five subsequently received (on a separate occasion) an infusion (6.5 mg kg^{-1}) at constant rate over 2h. Frequent venous blood samples were taken and plasma assayed for doxapram by g.l.c. The plasma doxapram concentration-time data after intravenous injection and after constant-rate intravenous infusion were fitted by a 3-compartment model. Mean ($\pm$ s.e.) terminal plasma half-lives (h) of 6.0 $\pm$ 1.4 and 7.4 $\pm$ 1.5 (n = 5), and mean total body clearances (ml min^{-1} kg^{-1}) of 6.5 $\pm$ 1.0 and 6.1 $\pm$ 0.7, after injection and after infusion respectively, did not differ significantly.

An intravenous regimen was sought to achieve rapidly and to maintain a constant plasma doxapram concentration of 2 μg ml^{-1}. One method (Vaughan & Tucker, 1976) required 4 simultaneous intravenous administrations; in addition the rapid bolus injection required produced very unpleasant side-effects. An empirical approach in which a constant-rate infusion of short duration was followed by an infusion at varying rate avoided this problem. Infusion rates during the latter period were calculated by analogue computer and converted to potentiometer settings on a variable-speed infusion pump; the setting was manually readjusted at the end of each 3-minute interval throughout the infusion.

Measured concentrations during the variable-rate infusion over 50 to 60 min were in good agreement with the desired concentration in 3 out of 6 trials (Table). The regimen, adjusted for body weight, was also used in a bronchitic patient and a mean concentration of 2.0 $\pm$ 0.17 μg ml^{-1} (n = 5) was found during infusion over 4h.

A simplified regimen is proposed for the intravenous administration of doxapram in which the infusion rate is successively reduced. For a drug with multi-compartmental distribution this appears preferable to one with successive increases, as currently recommended ("Dopram" Data Sheet, A.H. Robins, 1977), since the latter give rise to high concentrations during a prolonged infusion.

Table: Plasma doxapram concentrations (μg ml^{-1}) during variable-rate infusion.

Subject	1	2*		3*	
Mean	2.1	1.9	2.2	2.4	2.8	2.5
s.e.	0.06	0.20	0.09	0.15	0.08	0.06
n	8	5	3	4	8	4

* replicate trials

Robson, R.H. & Prescott, L.F. (1979) Br. J. clin. Pharmac. 7: 81-87
Vaughan, D.P. & Tucker, G.T. (1976) Eur. J. clin. Pharmac. 10: 433-440