proportionately at higher doses. Consequently total systemic blood clearance of pethidine (dose i.v./AUC i.v.) fell with increasing dose, the values for the three dogs at the 1.0 and 3.0 mg/kg i.v. doses being 59 and 34, 51 and 42, 65 and 52 ml min^{-1} kg^{-1} respectively. However a plot of β (the terminal disposition rate constant) $\times$ AUC against dose (i.v.) was linear, indicating that volume of distribution was a constant (values for each dog—4.2, 4.4 and 3.6 l/kg). This indicates that changes in clearance are reflected in changes in β. In two dogs a plot of $\beta \times$ AUC against dose (p.o.) was linear and the systemic availability of pethidine in these dogs, calculated as the ratio of the slopes of the p.o. and i.v. regression lines was 0.41 and 0.38. In the third dog $\beta \times$ AUC against dose was non-linear: thus availability changed with dose in this dog between 0.57 and 0.64 at the 2.0 and 3.0 mg/kg p.o. doses.

The findings in single dose administrations of pethidine were reproducible when further single doses were given. The clearance of pethidine in these animals approached liver blood flow and the low oral availability is compatible with significant 'first pass' hepatic metabolism of pethidine. In the repeated dose study for both i.v. and p.o. administration, no accumulation of pethidine occurred and the kinetics of pethidine did not change with time. The data suggest that while pethidine may exhibit dose-dependent disposition kinetics, there is no evidence for time dependent kinetics at the doses studied.

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Fluorimetric determination of ampicillin and cephalexin

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A fluorimetric method for quantitative analysis of two β-lactam antibiotics ampicillin and cephalexin has been developed, based upon the production of fluorescent derivatives formed by alkaline hydrolysis with 2N NaOH and heating at 100°C. The rate of formation of fluorescent material is enhanced by addition of formaldehyde in the buffer. The fluorescent compounds exhibit uncorrected excitation and emission spectra at 345 and 420 nm respectively. The structural similarities between the side chains of ampicillin and cephalexin and their identical fluorescent spectra suggest that both the antibiotics could be forming a similar fluorescent derivative. Although the precise chemical identity of the fluorescent derivative has not yet been determined, there is evidence to suggest that it may be the diketopiperazine derivative (Cohen, Funke & Puar, 1973; Indelicato, Narvilas, Pfeiffer, Wheeler & Wilham, 1974, 1974; Yamana, Tsuji, Kanayama & Nakono, 1974). An assay procedure based on these observations permits detection of less than 0.1 μg/ml of ampicillin and cephalexin in aqueous solution and plasma. Because of greater sensitivity, the proposed method is more suitable for clinical studies of these antibiotics than the previously described acid hydrolysis method for ampicillin (Jusko, 1971).

The results obtained with the fluorimetric assay have been compared with the results obtained in microbiological assay. The fluorimetric assay has advantage over microbiological assay in terms of ease and speed of performance, reproducibility and sensitivity.

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