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# Serum and peritoneal fluid concentrations of clindamycin and lincomycin in the mouse

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Serum concentrations of drug were obtained at various times after intramuscular dosing of healthy mice with either clindamycin or lincomycin hydrochlorides. Washings from the peritoneal cavity were taken at the same time as the serum samples. Changes in drug concentration in the peritoneal fluid with time mimic those for the serum, but concentrations in peritoneal fluid are much greater than the corresponding serum concentrations. The total volume of peritoneal fluid was estimated to be 0·05 ml.

The pharmacokinetic profile of clindamycin has been studied in man (Wagner et al 1968; De Haan et al 1972, 1973; Forist et al 1973). That for lincomycin has also been determined (Wagner et al 1965; Wagner 1967). These studies have shown that the overall rates can be described in terms of a one compartment model.

We have determined serum and peritoneal fluid concentrations of clindamycin and lincomycin in mice after intramuscular dosing. Physiologically it is to be expected that serum and peritoneal fluid would be described by the same pharmacokinetic compartment. However, the actual ratios of the two concentrations are of interest in judging whether these drugs may be of use in combating post operative abdominal infection.

## MATERIALS AND METHODS

Clindamycin hydrochloride and lincomycin hydrochloride were donated by Upjohn Limited. Sorensen's phosphate buffer solution (0·067 M, pH 7·4) was used.

Sodium pertechnetate injection (Tc-99m)B.P. activity 5$\mu$Ci ml$^{-1}$ was obtained from a Philips Deplat technecium generator.

Mice of LACA strain of either sex, 18–20 g, were starved for 24 h before being injected intramuscularly with 10, 20 or 30 mg kg$^{-1}$ clindamycin hydrochloride or 100 mg kg$^{-1}$ lincomycin hydrochloride. Groups of five animals were killed by cervical dislocation at various times after dosing and 1 ml of blood immediately collected from each animal by cardiac puncture. The blood samples were allowed to clot for 30 min before being centrifuged for 2 min at 12000$g$ to separate the serum, which was then pooled. Immediately after the heart puncture, the abdomen was opened and 0·5 ml buffer added to the peritoneal cavity. After 2 min agitation 0·2 ml of the wash buffer solution was removed and pooled.

### *Assay procedure*

The antibiotic content of the pooled serum and pooled peritoneal washing fluid samples were assayed using an agar plate diffusion method (Lees & Toothill 1955). The test organism was *Sarcina lutea* (PCI 1001) grown in tryptone soya broth and plated in agar (Difco Antibiotic Medium 1). The sample size was 0·08 ml. The plates were left to stand for 3 h at room temperature (20 °C) before incubation at 37 °C for 18 h. Zones of inhibition were measured to the nearest 0·1 mm. Concentrations corresponding to the zones were calculated from a calibration curve obtained using the standard values on the same plate. There was little difference between calibration curves obtained on different occasions.

### *Estimation of peritoneal fluid volume*

Estimation of the comparatively large amounts of peritoneal fluid produced in experimental peritonitis can be made by direct aspiration of the fluid (Munoz 1957). However, it is difficult to quantify the normal volume of peritoneal fluid in the mouse or other small mammals by aspiration since the volume removed is small and the volume remaining is a significant proportion of the whole. Instead, preliminary investigations of the volume were made by an isotope dilution technique. Mice were killed and a small incision made in the peritoneal wall, 0·5 ml of a technetium isotope solution of known radioactivity was placed inside and the abdomen shaken for 2 min. A known volume of the washing was then withdrawn and assayed for radioactive content.

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## RESULTS AND DISCUSSION

The initial estimation of the peritoneal fluid volume showed no change in technetium concentration following mixing of a known concentration with peritoneal fluid in situ. It was concluded that the total volume of peritoneal fluid is less than 0·05 ml.

Pharmacokinetic analyses based on serum or urine determinations generally reveal information about the amount of drug absorbed, rate of absorption and elimination, and the model which best describes these rates. While it may be reasonable to base models on a compartmental system, the limitations of any such model must be realized. By definition, a compartment consists of a set of tissues which are in rapid equilibrium with each other. The model does nothing to establish the number of tissues in the set, nor very much towards defining what they are. Furthermore, the only statement a model makes about intra-compartmental distribution is that it takes place very rapidly compared with inter-compartmental rates. It says nothing about the actual concentrations reached in the various tissues. Thus for a compartment for which the variation of drug concentration with time in one tissue, say blood, has been determined, the concentration-time profiles of the drug in other tissues in the compartment will have the same shape as that for blood but may be many times larger or smaller.

The change in serum concentrations of clindamycin with time is shown in Fig. 1a. Results are shown as the mean with standard deviation for doses of 10 and 20 mg $kg^{-1}$, n = 6 samples, each time with pooled serum from five animals. Results for the 30 mg $kg^{-1}$ dose are shown as the mean only, the experiment having been carried out twice. The results from the two lower doses are plotted as log concentration versus time in Fig. 2, and show a slight divergence in elimination rate between the two sets of results. This divergence is readily apparent in the plot for the 30 mg $kg^{-1}$ dose and suggests the saturation of a mechanism of elimination at doses above about 20 mg $kg^{-1}$.

The change in serum concentrations in each case is mimicked by the change in the peritoneal fluid values (Fig. 1b), showing that the two body constituents can be regarded as belonging to the same kinetic compartment. That the actual concentrations in serum and peritoneal washings are the same is purely fortuitous; use of a different volume of isotonic buffer to wash out the peritoneum would have produced a different concentration. Lincomycin, which was determined by methods similar in all respects to clindamycin, also shows a parallelism between concentrations in serum and peritoneal fluid (Fig. 3) though in this instance its concentration in the peritoneal fluid washings is about twice that in the serum.

Comparative concentrations of clindamycin in serum and other body tissues in man have been reported for bone (Vacek et al 1972), saliva (Quayle & Whitmarsh 1972) and synovial cavity (Deodhar et al 1972). An oral dose of clindamycin in man is rapidly absorbed (Wagner et al 1968) and measurable values in bone, saliva and synovial fluid are reached within 1 h. These are less than the corresponding serum concentrations by a factor of 2–10. In abscesses induced in the mouse, clindamycin concentra-

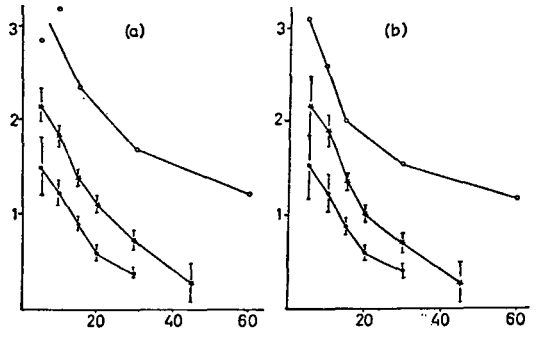


FIG. 1. Variation in 1(a) serum and 1(b) peritoneal fluid washing concentrations of clindamycin with time following i.m. administration of clindamycin HCl in mice. Doses of clindamycin hydrochloride were 10 (●); 20 (×) and 30 (○) mg $kg^{-1}$. Ordinate: clindamycin ($\mu$g $ml^{-1}$). Abscissa: time (min).

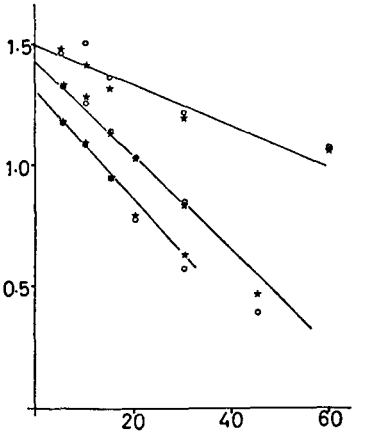


FIG. 2. Log concentration versus time for clindamycin concentrations in (○) serum and (×) peritoneal fluid washings following i.m. administration of clindamycin HCl to mice of 10, 20 and 30 mg $kg^{-1}$. Ordinate: lincomycin ($\mu$g $ml^{-1}$). Abscissa: time (min).

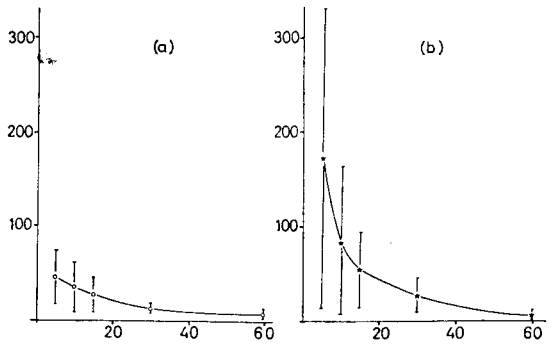


FIG. 3. Variation in serum (○) and peritoneal fluid washings (×) of lincomycin concentrations with time following i.m. administration to mice of lincomycin HCl 100 mg $kg^{-1}$. Ordinate: log (10 + clindamycin concentration). Abscissa: time (min).

tions were higher than in blood by a factor of 8–10 (Wilkins et al 1977). In a study of the penetration of a number of antibiotics (not including clindamycin or lincomycin) into peritoneal fluid in rabbits presenting experimental peritonitis, MacGregor (1977) found that the time courses of the concentrations in peritoneal fluid resembled those in serum but that the concentrations were somewhat higher (factor 2) after the initial intravenous infusion had ceased.

The results of the present study are in accord with the findings of MacGregor (1977) although the animals we used were normal and had no evidence of peritonitis. The relative concentration of clindamycin in the peritoneal fluid washings follows the same time course as that in the serum at all three doses investigated. The concentration–time profile of clindamycin in peritoneal fluid washing is comparable to that in serum. Since the phosphate buffer dilutes the peritoneal fluid by at least 50 times, the concentration of antibiotic in the peritoneal fluid must necessarily be at least 50 times that of the serum.

Similar considerations apply to lincomycin. Results, shown as mean with standard deviation, for serum values and for the concentrations in the peritoneal fluid washings following a dose of 100 mg $kg^{-1}$ lincomycin hydrochloride are plotted in Fig. 3 (a and b) and show a much greater degree of variation at individual times than when clindamycin is used, though the variations in the calibration curves for the two drugs were similar. It would seem, therefore, that the disposition of lincomycin within the animal is more liable to individual differences than is so for clindamycin. Despite these variations, the similarity between changes in serum concentration and concentration in peritoneal fluid washings is marked. With lincomycin, however, the concentrations in the peritoneal fluid washings are greater than in the serum at corresponding times, suggesting that the level of drug in peritoneal fluid is 50–100 times greater than that in the serum.

The concentrations of the antibiotics achieved are well above the stated therapeutic values. However, it might be pertinent to ask whether it is the concentrations or the absolute amounts of the antibiotics that is relevant to their bacterial action.

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