interval after dosing. Mexiletine was continued in a regimen of 200 mg every 8 h. In addition, dialysate was collected 6 days into therapy in order to assess steady-state dialysis drug recovery. Steady-state serum drug levels were also drawn at this time. Biological samples were analyzed for mexiletine content using a modification of the gas chromatographic method of Smith & Meffin (1980). Clearance data and amount cleared by CAPD at steady state were calculated using standard methods (Gibaldi & Perrier, 1982).

Calculated clearances (total body, dialysis, and renal) and amount cleared daily by CAPD at steady state are presented in Table 1. Samples of dialysate from this patient prior to receiving the drug demonstrated no assay interferences. The results indicate that peritoneal dialysis removes very little mexiletine. The total body clearance was similar to that reported previously in renal failure patients (Jones et al., 1983; El Allaf et al., 1982). It must be recognized that this is an apparent total body clearance since the fraction absorbed had to be estimated (88%). The minimal amount of drug removed daily by CAPD as noted by Jones et al. (1983) (5 mg) was similarly noted in our patient (17 mg).

At present, we believe that the dosage of mexiletine in a patient on peritoneal dialysis does not have to be routinely altered from that recommended for patients with severe renal impairment not on such dialysis. In most cases, this dosage regimen will be similar to that used in patients with normal renal function, although individualized dosage adjustment based upon serum concentration determinations and clinical response should be routinely performed.

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Effect of ranitidine on procainamide disposition

In a recent volume of the Journal, Somogyi & Bochner (1984) have provided evidence that ranitidine reduces the renal clearance of procainamide (PA) and that of its major metabolite N-acetylprocainamide (NAPA). Evidence to support their contention that ranitidine also reduces the absorption of procainamide is much less convincing.

Their evidence is based on the consideration that if all factors other than renal clearance of
PA remain constant, then the hepatic clearance of PA divided by its bioavailability (CL$_{H}$/F) should show no change. According to Somogyi & Bochner (1984), their calculations revealed a considerable change in CL$_{H}$/F which decreased from 90 ml/min to 67 ml/min when ranitidine was present and this they attributed to reduced absorption of PA. Whereas they use the symbol F to represent bioavailability, they relate this to ‘the fraction of the dose absorbed’—or in practical terms to ‘the value of the combined cumulative excretion of PA and NAPA’ which was found to decrease from a mean of 77.8% to 70.8% of the dose in the presence of ranitidine.

The calculation employed was based on the relationship

$$\text{CL}_H = \text{CL} - \text{CL}_R$$  \hspace{1cm} (1)

where CL and CL$_R$ represent respectively the total systemic clearance and the renal clearance of procainamide.

In relating the terms in equation (1) to the experimental data, it is necessary to consider whether the factor for bioavailability is already incorporated in the method of calculation or whether further adjustment is required.

In terms of the oral data, the term for renal clearance already includes a factor for bioavailability as seen from the relationship,

$$\text{CL}_R = \frac{\text{fe}.D_{iv}}{\text{AUC}_{iv}} = \frac{\text{fe}.F.D_{p.o.}}{\text{AUC}_{p.o.}} = \frac{\text{Ae} (\infty)_{p.o.}}{\text{AUC}_{p.o.}}$$  \hspace{1cm} (2)

where F the bioavailability is the fraction of the oral dose of PA that reaches the systemic circulation in unchanged form, fe is the fraction of the systemically available drug that is excreted unchanged in urine, D$_{iv}$ and D$_{p.o.}$ are, respectively, an intravenous dose and oral dose of procainamide, Ae ($\infty$)$_{p.o.}$ is the total amount of unchanged procainamide excreted in the urine after oral dosage, and AUC$_{iv}$ and AUC$_{p.o.}$ are respectively the areas under the curve of the plasma concentration of procainamide vs time plot after intravenous and oral dosage.

The term for total clearance does however require adjustment, as apparent from the relationship,

$$\text{CL} = \frac{D_{iv}}{\text{AUC}_{iv}} = \frac{F.D_{p.o.}}{\text{AUC}_{p.o.}}$$  \hspace{1cm} (3)

It follows that hepatic clearance calculated using equations (2) and (3) will include the factor F.

$$\text{CL}_H = \frac{F.D_{p.o.}}{\text{AUC}_{p.o.}} - \frac{\text{Ae} (\infty)_{p.o.}}{\text{AUC}_{p.o.}}$$  \hspace{1cm} (4)

Equation (4) cannot be rearranged to isolate the fraction CL$_{H}$/F utilised by Somogyi & Bochner (1984), but leads directly to CL$_H$, if the value of F were known. Manion et al. (1977) found that the absolute bioavailability of PA from the product used in their study had a mean value of 83. Applying this value to equation (4) together with the data of Somogyi & Bochner (1984) gives a value for CL$_H$ of 159 ml/min for PA on its own and 163 ml/min when given with ranitidine. No marked change in CL$_H$ is apparent. The calculated value of CL$_H$ is dependent on the value assigned to F and this can exhibit slight variation from one occasion to another, but on the evidence presented it is not necessary to postulate a change in the bioavailability or extent of absorption of PA when ranitidine is added to the regimen.

An explanation for the lower urinary recovery of the two metabolites when ranitidine is administered with PA is required however. Apart from elimination as PA and NAPA, other metabolites account for about 15% of an oral dose of PA. These include p-amino-benzoic acid (duSouich & Erill, 1977; Giardina et al., 1976), desethylprocainamide (Ruo et al., 1981) and their acetylated forms. The extent to which a drug is excreted in the urine is a function of its urinary excretion rate constant relative to the rate constants governing its elimination by other routes. Consequently when the urinary excretion of PA and

![Figure 1](image-url)  \hspace{1cm} Figure 1 The effect of partially blocking the urinary excretion of PA and NAPA results in a lower urinary recovery of these compounds.
NAPA is partially blocked by ranitidine, the excretion rate constants of these compounds are reduced during this period, a higher percentage of these compounds will be eliminated by metabolism, and a smaller percentage will appear in the urine as PA and NAPA. This is depicted diagrammatically in Figure 1.

The urinary recovery of PA and NAPA cannot therefore be used as a relative measure of the bioavailability of PA, nor does it provide a reliable estimate of the amount of drug absorbed.

The authors present their findings based on the mean values of all volunteers, but the mean value can be totally atypical of the pattern of any one volunteer. This is particularly relevant in respect of procainamide that is known to exhibit polymorphic acetylation (Reidenberg et al., 1975). It is noted that the subjects in this study remained 'supine or seated' for the first 2 h following the procainamide dose. The posture of the subject can influence both the rate of drug absorption and the extent of the first pass effect and, in the interest of precision, consideration could therefore be given to greater control of this factor.

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Correction equation for ECG time intervals

I have read with interest the letters from Kelman et al. (1984) and Staniforth (1984) discussing the analysis of data presented in Staniforth (1983). Dr Staniforth may have misunderstood the most important points made by Kelman et al. (1984) and seems to have failed to answer their criticisms. The analysis of repeated observations on several individuals is not easy in the best circumstances and when unequal numbers of observations are made on different individuals then the analysis is often almost impossible.

Kelman et al. (1984) have given a clear illustration of the totally invalid 'results' which can be obtained when the structure of the data is ignored. Neglect of the structure of data leads to very much more invalid analysis than incorrect assumptions for t-tests or other topics cited in elementary textbooks. A further culprit is the use of computer programs whether on laboratory computers, microcomputers or even well designed statistical program packages on large computers. These programs will accept data and produce convincing looking results whatever the data structure of the original experiment.

Mainland (1963) gives an extremely clear discussion of the topic and includes the following sentence 'To anyone with a biological upbringing this must be a fantastic concept, unless he has been hoodwinked by an elementary statistics book that has led him to believe that, if he has found no 'statistically significant' difference between the averages for the various (dogs), he