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ALTERED DISTRIBUTION OF DIGOXIN IN RENAL FAILURE—A CAUSE OF DIGOXIN TOXICITY?

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1 Three cases are described in which renal failure was accompanied by a lowered apparent volume of distribution of digoxin. In two cases this resulted in frank digoxin toxicity and in one equivocal toxicity. In all three cases digoxin plasma levels were greater than 2 ng/ml.

2 The possible causes of the abnormal distribution of digoxin in renal failure are discussed.

3 Recommendations are outlined for the use of digoxin in patients with renal failure aimed at circumventing the problem raised by a lowered apparent volume of distribution of the drug.

Introduction

It is generally assumed and has been stated by both Jelliffe (1968) and Moe & Farah (1975) that the loading dose of digoxin in patients with renal failure should be similar to that administered to patients with normal renal function; this view has recently been supported by Wagner (1974). Chung (1969), however, has suggested that patients with renal impairment should receive only a half to two-thirds of the usual loading dose and this view has been supported by Reuning, Sams & Notari (1973) and Jusko, Szefler & Goldfarb (1974) on pharmacokinetic grounds. We present three case reports which support the latter opinion.

Case 1

A 63-year-old woman weighing 57 kg was admitted with accelerated hypertension, acute renal failure and left ventricular failure. She received digoxin (1 mg) orally over 3 days, was noted during that time to have bouts of nodal rhythm and digoxin was discontinued. A diagnosis of renal artery stenosis was made and 2 weeks after her last dose of digoxin she received a right renal artery graft. Immediately postoperatively she was given digoxin (0.5 mg) intravenously (8.8 μg/kg). Figure 1 shows her subsequent plasma digoxin levels (measured by radioimmunoassay). At that time her half-time of elimination of the drug from the plasma ($T_{\frac{1}{2}\beta}$) was 93 h consistent with a creatinine clearance of 0 ml/min (Jelliffe, 1968) and her apparent volume of distribution (V_d) 125 litres or 2.2 litres/kg. She was anuric and was being treated by haemodialysis; her plasma potassium levels are also shown in Figure 1 and the arrhythmias which she had are indicated at their times of occurrence. The various arrhythmias occurred (a) when her plasma digoxin levels were high and (b) when her plasma potassium levels were below normal at times when the plasma digoxin levels were therapeutic; only when plasma digoxin levels were therapeutic and potassium levels normal did she revert to sustained sinus rhythm. The arrhythmias did not respond or responded only transiently to treatment with diphenylhydantoin, atropine, calcium gluconate and isoprenaline. Other drugs which she received were potassium chloride and gentamicin. Two weeks later, when digoxin was reintroduced, plasma levels following a single oral dose of 0.25 mg indicated a $T_{\frac{1}{2}\beta}$ of 61 h (consistent with her creatinine clearance at that time of 36 ml/min) and a V_d of 2.77 litres/kg. A maintenance dose of 0.125 mg once daily orally was prescribed and when her renal function had returned to normal her steady state plasma digoxin level was 0.5 ng/ml indicating a V_d of 349 litres (6.1 litres/kg). (For details of the mathematics and assumptions involved see appendix; the clinical and pharmacokinetic data for all three cases are summarized in Table 1.)

Case 2

A 56-year-old man weighing 77 kg was admitted with an acute anterior myocardial infarct having had a previous myocardial infarct 2 years before.

Table 1 Clinical and pharmacokinetic data of the three cases with normal values for comparison (see Appendix for calculations and assumptions involved)

	Weight (kg)	*Dose, mg (μg/kg)*	*Dose corrected for absorption, mg (μg/kg)*	*Route and period of administration*	*Plasma creatinine (mg%)*	*Creatinine clearance (ml/min)*	$T_{½\beta}$ *(h)*	V_d, *litres (litres/kg)*
Case 1	57							
(a)		0.5 (8.8)	0.5 (8.8)	i.v. bolus	5.86	Anuric	93	125 (2.2)
(b)		0.25 (4.4)	0.168 (2.9)	Single oral dose	1.37	36	61	158 (2.8)
(c)		0.125 (2.2)	0.084 (1.5)	Daily oral dose	0.67	–	Assumed 38	349 (6.1)
Case 2	77							
(a)		1.0 (13.0) then 0.25 (3.2)	0.67 (8.7) then 0.208 (2.7)	Orally in three divided doses over 28 h then i.m. bolus	2.03	–	37.9	264 (3.4)
(b)		0.125 (1.6)	0.084 (1.1)	Daily oral dose	1.37	41	Assumed 37.9	349 (4.5)
Case 3	55	0.35 + 0.25 (9.1) then 0.5 (9.1)	0.482 (8.8) then 0.335 (6.1)	One dose i.v., one dose i.m. then single oral dose	2.60	–	34.7	83 (1.5)
Normal					0.8-1.7	100-120	Average 38 (Jelliffe, 1968)	Average 570 (Koup, Greenblatt *et al.*, 1975)

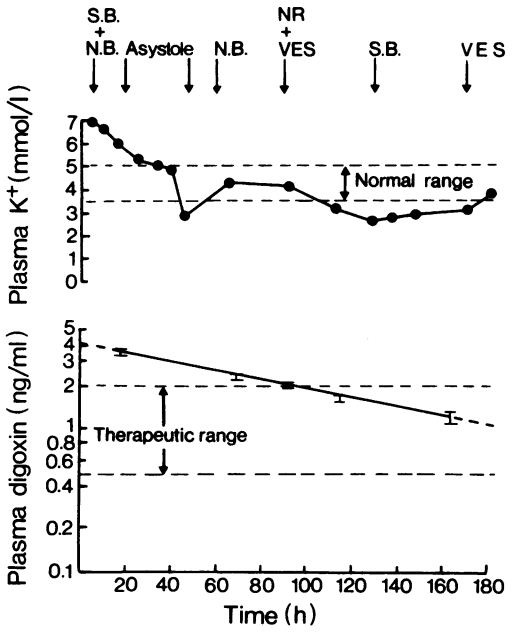

Figure 1 Plasma potassium and digoxin levels in case 1 (J.M., 57 kg) following a single i.v. dose of digoxin (0.5 mg). Digoxin levels are the mean ± s.e. mean of four estimations. Digoxin $T_{\frac{1}{2}}$ = 93 h, V_d = 125 litres (2.19 litres/kg). SB, sinus bradycardia; NB, nodal bradycardia; NR nodal rhythm; VES, ventricular extrasystoles.

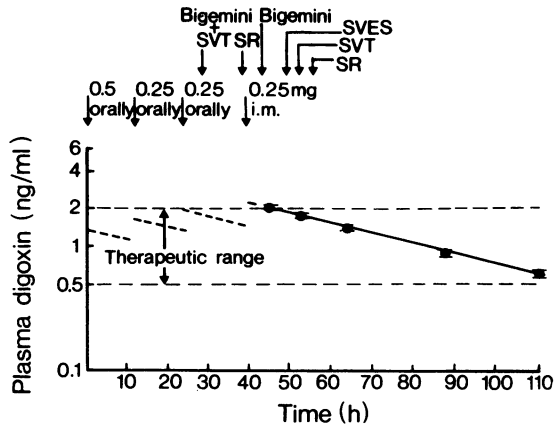

Figure 2 Plasma digoxin levels in case 2 (J.B., 77.4 kg) following four doses of digoxin. The dotted lines indicate the theoretical plasma levels during the periods of administration of the individual doses assuming instant distribution of the drug after administration. Digoxin $T_{\frac{1}{2}}$ = 37.9 h, V_d = 264 litres (3.4 litres/kg). SVT, supraventricular tachycardia; SR, sinus rhythm; SVES, supraventricular extrasystoles.

He had pulmonary oedema due to left ventricular failure which partly responded to treatment with frusemide and diamorphine and he had occasional ventricular extrasystoles which were controlled with small doses of lignocaine. On admission he was in mild renal failure and over the next 36 h this deteriorated to the point where his plasma urea was 125 mg% and creatinine 2.03 mg%. At that time he was given a total of 1 mg of digoxin orally (13 μg/kg) in three divided doses and shortly after the third developed the various arrhythmias which are shown in Figure 2; just before a further dose of 0.25 mg intramuscularly, however, he had reverted to sinus rhythm and following that dose he once more developed various arrhythmias. Treatment at different times with intravenous procainamide and intravenous and oral practolol did not affect his arrhythmias and he had already reverted to sinus rhythm when only one dose of diphenylhydantoin (50 mg) had been given orally. Other drugs which he received were heparin, warfarin, ampicillin, potassium chloride and diazepam. His plasma digoxin levels following the fourth dose of digoxin are shown in Figure 2. Only when the plasma digoxin level fell below 1.7 ng/ml was he free from arrhythmias. His $T_{\frac{1}{2}\beta}$ was 37.9 h and his V_d 264 litres (3.4 litres/kg). At a later date when his renal function had improved slightly (urea 47 mg%, creatinine 1.37 mg%, creatinine clearance 41 ml/min) his steady-state plasma level on a reintroduced daily maintenance dose of 0.125 mg orally was 0.5 ng/ml indicating a V_d of 349 litres (4.5 litres/kg).

Case 3

A 61-year-old man weighing 55 kg who had suffered from intermittent angina for 6 months was admitted with an acute inferior infarct and left ventricular failure. His plasma urea and electrolytes were normal on admission but over the subsequent 3 days his renal function deteriorated and on the first day of plasma digoxin determination his urea was 126 mg% and creatinine 2.6 mg% with plasma sodium 126 mmol/l, potassium 6.6 mmol/l, chloride 86 mmol/l and bicarbonate 26 mmol/l. He was given digoxin (0.5 mg) (9.1 μg/kg) parenterally (0.25 mg intravenously and 0.25 mg intramuscularly) and sub-

sequently complained of nausea, vomiting and feelings of dizziness; a bout of ventricular extrasystoles responded to treatment with lignocaine intravenously. Thirty-two hours after the initial dose he was given a further 0.5 mg orally and the plasma digoxin concentration 19 h later was 3.1 ng/ml. Subsequent plasma digoxin estimations revealed a $T_{\frac{1}{2}\beta}$ of 34.7 h and his V_d was calculated to be 83 litres (1.5 litres/kg). Other drugs which he received were frusemide, propranolol, atropine, diamorphine, heparin, diazepam and prochlorperazine.

Discussion

The apparent volume of distribution of digoxin in renal failure has been shown to be reduced in studies using both one-compartment (Reuning *et al.*, 1973) and two-compartment (Koup, Jusko, Elwood & Kohli, 1975; Reuning *et al.*, 1973) open model analysis. The ranges of values for patients in renal failure were 230-430 litres (mean 360) (Reuning *et al.*, 1973) and 236-481 (mean 328) (Koup, Jusko *et al.*, 1975) compared with quoted normal values of 420-1026 (mean 570) (Koup, Greenblatt, Jusko, Smith & Koch-Weser, 1975). Such reduction results in higher plasma levels than would be expected following the usual loading doses used in patients with normal renal function; the clinical significance of these higher levels, however, is in dispute. Reuning *et al.* (1973) have argued that the higher plasma levels reflect higher myocardial levels and that therefore lower loading doses of digoxin should be administered to patients in renal failure. Wagner (1974) on the other hand has suggested that this is not the case and that usual loading doses should be given though he maintains that the commonly recommended loading doses are too high and suggests an oral loading dose of 0.625 mg (about 9 μg/kg for a 70 kg patient).

There is little experimental evidence to support either viewpoint conclusively. Jusko & Weintraub (1974) have shown that the myocardial : serum concentration ratio of digoxin decreases with decreasing renal function and Jusko (1974) has reviewed the literature from which data on myocardial : serum concentration ratios can be culled and has found similar correlations. These data would support Wagner's contention. Coltart, Güllner, Billingham, Goldman, Stinson, Kalman & Harrison (1974), however, have shown in three patients, one of whom had a blood urea nitrogen of 60 mg%, that while plasma levels do not readily reflect total myocardial digoxin content they are almost identical with microsomal digoxin content. In addition Marcus, Peterson, Salel, Scully & Kapadia (1966) have shown that dogs in renal failure (due either to nephrectomy or ureteric ligation) have higher plasma levels and higher myocardial digoxin content following the administration of a dose of tritiated digoxin. These data would support the view of Reuning *et al.* (1973).

The first two patients we report here showed digoxin toxicity as judged by the criteria of Beller, Smith, Abelmann & Hood (1971) and the third possible toxicity. All had plasma digoxin levels greater than 2 ng/ml at least 6 h after a dose, following usual loading doses, due to lowered apparent volumes of distribution associated with renal failure. The occurrence of toxicity in these patients strengthens the arguments of Reuning *et al.* (1973) and suggests that in some patients with renal failure high plasma levels reflect elevated levels at the site of action of the drug; the fact that there are no previous reports of such cases seems to suggest, however, that not all patients may be so affected despite lowered apparent volumes of distribution.

The causes of this lowering of the apparent volume of distribution are as yet unknown. In Table 2 we have listed various abnormalities which might produce such an effect. Hyperkalaemia reduces the binding to and thus the inhibition of Na^+–K^+–ATPase (sodium and potassium linked magnesium dependent adenosine triphosphatase) by digoxin (Offerhaus, Aronson & Grahame-Smith, unpublished observations; Goldman, Coltart, Friedman, Nola, Berke, Schweizer &

Table 2 Possible causes of the lowered apparent volume of distribution of digoxin in renal failure (See text for discussion)

A	Associated with normal or low myocardial digoxin levels Hyperkalaemia
B	Associated with high myocardial digoxin levels (1) Poor peripheral tissue perfusion (excluding heart). (2) Diminished tissue mass—kidney, muscle, red cells, body fluids.
C	Associated with increased myocardial sensitivity to digoxin Diminished Na^+–K^+–ATPase activity.

Harrison, 1973) but would probably result in lowered myocardial concentrations and thus no toxicity—this might be a contributing factor in some patients. Altered distribution of some drugs may be attributable to altered tissue perfusion (Wilkinson, 1975); in patients suffering from peripheral circulatory failure this might be important and would lead to high cardiac concentrations if cardiac perfusion were normal. Cardiac failure *per se* does not influence serum levels, turnover and excretion rates of intravenously administered [^{3}H]-digoxin (Marcus, Kapadia & Kapadia, 1964; Doherty, Flanigan, Patterson & Dalrymple, 1969) but there are no data on changes in V_d. Alterations in peripheral tissue perfusion following treatment of cardiac failure in the patients reported here might have contributed to the subsequent increases in V_d observed (Table 1). Diminished tissue mass would lead to a lowered volume of tissue available for distribution but would not explain the return to normal of the volume of distribution in case 1 without change in weight or red cell mass as judged by haematocrit and haematological indices.

An interesting possibility is suggested by the work of Welt, Cole and their associates (Welt, Smith, Dunn, Czerwenski, Proctor, Cole, Balfe & Gitelman, 1967; Cole, Balfe & Welt, 1968; Cole, 1973). They have found that the plasma of uremic patients contains a dialysable substance which inhibits Na^+–K^+–ATPase activity in normal human erythrocytes but that this inhibition occurs predominantly when the plasma is that of uremic patients with high intraerythrocytic sodium concentrations (Cole *et al.*, 1968). Na^+–K^+–ATPase activity in the erythrocytes of patients with renal failure was also found to be diminished when compared with controls particularly in those patients with high intraerythrocytic sodium content (Cole, 1973). Furthermore the residual Na^+–K^+–ATPase activity is as sensitive to inhibition with ouabain as is the enzyme obtained from normal erythrocytes (Welt *et al.*, 1967). Erythrocytic Na^+–K^+–ATPase behaves like myocardial Na^+–K^+–ATPase and there is evidence to suggest that the toxic effects of cardiac glycosides are produced by inhibition of this enzyme (for review see Schwartz, Lindenmayer & Allen, 1975). If that is so, less digoxin would be required to cause toxic inhibition of the enzyme in uremic patients with elevated intraerythrocytic sodium levels than in other uremic patients or those without renal failure. This speculation, if correct, would account for the apparent low incidence of cases such as we have reported (only 25% of Welt and co-workers' patients (Welt *et al.*, 1967) had intraerythrocytic sodium concentrations greater than 12 mmol/l) and would account for the overlap in apparent volumes of distribution of normal and uremic patients (Koup, Jusko *et al.*, 1975).

The data which we have presented here have been limited by the restrictions of clinical practice and in the appendix we have outlined the major shortcomings of the pharmacokinetic calculations we have made. However, despite the difficulties in deriving accurate estimates of the true apparent volumes of distribution involved, the changes we have observed are too large merely to be accounted for by pharmacokinetic inaccuracies; indeed, any over-estimation of the true volumes strengthens the argument. We believe that the changes we have observed are real and have contributed to the digoxin toxicity which occurred in these patients. Further characterization of the cause of the abnormal distribution of digoxin in renal failure by more precise prospective clinical studies is required. In view of the cases we have presented here we would meantime make the following recommendations: an oral loading dose of between 12 and 20 μg/kg lean body weight will produce plasma digoxin levels in the therapeutic range in patients without renal failure (Aronson & Grahame-Smith, 1976); in patients with renal failure we would recommend reducing this loading dose by up to half, incrementing with additional doses only if the therapeutic response is judged not to have been achieved; it is far safer to keep increasing the dose in this way than to treat established digoxin toxicity in a patient with renal failure. Maintenance dosage may be calculated as a percentage of the loading dose found to be required, the percentage being based on renal function, in particular creatinine clearance (Jelliffe, 1968). Plasma digoxin measurement, where available, can be of help in monitoring therapy.

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Appendix

(a) Pharmacokinetic calculations

V_d after intravenous administration has been calculated from the relationship $V_d = Dose/B$ where B is the theoretical plasma level at zero time assuming instant distribution in a one-compartment model and is found by extrapolating the plasma level-time exponential (Figure 1) back to the ordinate.

V_d after oral and intramuscular administration has been calculated using the relationship:

$$V_d = \frac{\text{total body digoxin content at time } t}{\text{plasma level at time } t}.$$

Total body digoxin content has been calculated assuming 67% absorption after oral administration (Doherty & Kane, 1976) and 83% after intramuscular administration (Greenblatt, Duhme, Koch-Weser & Smith, 1973) and the percentage of the administered dose present at time t calculated assuming that $T_{\frac{1}{2}\beta}$ (the half-time of disposition of the drug after distribution has taken place) is equal to that actually measured after time t (e.g. after 44 h in Figure 2).

V_d at steady state (V_d^{ss}) have been calculated using the relationship (Wagner, Northam, Alway & Carpenter, 1965):

$$V_d^{area} = \frac{F \cdot D}{C^{ss} \cdot \beta \cdot \tau} \text{ ml; then (for digoxin)}$$

$$V_d^{ss} = 0.914 \times V_d^{area} \text{ (Wagner, 1974)}$$

where F = fraction of oral dose absorbed (0.67 as above)

D = daily maintenance dose (ng)

C^{ss} = average steady state plasma level (ng/ml)

$\beta = \ln 2 / T_{\frac{1}{2}\beta}$ (h^{-1})

$\tau = 24$ h

(b) *Shortcomings of the pharmacokinetic calculations*

Because of the need to calculate the apparent volume of distribution in these patients in different clinical settings there are some shortcomings regarding the above calculations and the data listed in Table 1.

V_d calculated assuming a one-compartment open model is inaccurate but *over*-estimates the true V_d (Wagner & Northam, 1967). V_d^{ss} as calculated here is model-independent.

The percentage absorption of digoxin after oral administration may be lower than normal in the presence of renal failure but there are no data available on this matter. All digoxin administered to these patients was Lanoxin (Burroughs Wellcome) of post-1972 formulation which would be expected to afford high bioavailability. We have therefore chosen to assign F the value of 0.67; indeed, if absorption is impaired lower values of F would give even lower estimates of V_d^{oral} and V_d^{ss}. Similarly, the degree to which increased metabolism (Marcus *et al.*, 1966) or increased hepato-biliary recirculation of digoxin (Doherty, Perkins & Wilson, 1964) might affect the figures is incalculable; the latter would probably result in an *under*-estimate of the true V_d, if at all, while the former would result in an *over*-estimate.

Certain other assumptions have had to be made in some instances (see Table 1) where data were not available and these inevitably reduce the accuracy of the calculations.

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