LOADING DOSE OF DIGOXIN IN RENAL FAILURE

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- 1 Twenty-two dialysis dependent patients received an intravenous loading dose of digoxin of 10 µg/kg and the mean $\pm$ s.d. serum digoxin concentration 24 h later was 1.5 ng/ml $\pm$ 0.4 (range 0.8–2.1 ng/ml). No evidence of toxicity was observed.
- 2 The average apparent volume of distribution of digoxin in dialysis dependent patients was found to be reduced by about one third compared with that reported for individuals with normal renal function, but there was great variation.
- 3 An appropriate intravenous loading dose of digoxin in most patients with advanced renal failure is 10 µg/kg.

Introduction

There is controversy concerning the appropriate loading dose of digoxin in renal failure. Some authors (Jelliffe, 1968; Moe & Farah, 1975; Wagner, 1974) suggest the dose should be similar to that given patients with normal renal function and others (Aronson & Grahame-Smith, 1976; Chung, 1969; Reuning, Sams & Notari, 1973) recommend that the loading dose be reduced by $\frac{1}{3}$ – $\frac{1}{2}$. This suggestion may be supported by reports of a reduction in the average apparent volume of distribution (V_{dapp}) (Gault, Jeffrey, Chirito & Ward, 1976; Koup, Jusko, Elwood & Kohli, 1975; Reuning *et al.* 1973; Van der Vijgh & Oe, 1977). A decrease in the myocardial to serum digoxin concentration ratio in renal failure has also been reported (Jusko & Weintraub, 1974). The significance of these reports in terms of digoxin dosage, blood levels and toxicity remains uncertain, particularly as evidence has been presented suggesting that tolerance to digitalis is increased in uremic patients (Kramer, Stroh, Matthei, Teiwes & Scheler, 1978).

We report serum digoxin concentrations taken serially up to 24 h after i.v. injection of 10 µg/kg in 22 patients with acute, or dialysis dependent chronic renal failure, use these data to calculate values for V_{dapp} and review reports on the V_{dapp} of digoxin in patients with renal failure.

Methods

The digoxin loading dose was calculated on the basis of 10 µg/kg and administered in 50 ml, 5% dextrose

and water over 20–30 min using Lanoxin brand of digoxin (Burroughs Wellcome Co., Research Triangle Park, N.C.). No further digoxin was given or dialysis performed for the next 24 h. Bloods were drawn in all 22 patients 24 h after the start of the digoxin infusion, in 9 patients after 15 min, in 11 after 30 min, in 14 after 1 h, in 9 after 2 h and in 15 after 8 h.

The usual indication for digitalization was pulmonary oedema which was resistant to fluid removal by dialysis, in a patient with hypertensive and/or arteriosclerotic heart disease. Fluid overload of varying severity was invariably present. All patients were in sinus rhythm except for one who had atrial fibrillation.

Six patients were female and 16 male. Four patients suffered from acute renal failure which had been established for several days and 18 from end stage chronic renal disease requiring dialysis. Creatinine clearance was < 5 ml/min in all patients. Their ages ranged from 20 to 82 years (mean 51) and body weight from 44 to 89 kg (mean 66 kg).

Serum digoxin concentration was determined by radioimmunoassay using tritiated digoxin and reagents prepared by Kallstadt Laboratories (Minneapolis, Minn.), as previously described (Gault *et al.*, 1976). Hematocrit, serum sodium, potassium, chloride, CO₂, calcium, inorganic phosphorus, total protein, albumin, creatinine and body weight were determined within 24 h of the time of the digitalizing dose. Standard Autoanalyzer I methodologies (Technicon Corp., Tarrytown, N.Y. 10591) were used to determine the biochemical parameters on venous blood, handled in part aerobically.

V_{dapp} was estimated by dividing the digoxin dose

Figure 1 Mean values for serum digoxin concentrations with standard deviations are shown at intervals for 24 h after i.v. injection of a loading dose of 10 µg/kg digoxin. All patients had advanced renal failure and required dialysis.

by the serum digoxin concentration at 8 and 24 h and also by backplotting to obtain a theoretical zero-time digoxin concentration using the 24 and 8 h serum digoxin concentrations (β phase).

Results

The mean values and s.d. for serum digoxin concentration at 15 and 30 min and 1, 2, 8 and 24 h after administration of digoxin are shown in Figure 1. The mean $\pm$ s.d. value after 8 h was 1.7 ± 0.6 ng/ml and after 24 h, 1.5 ± 0.4 ng/ml with a range of 0.8 to 2.1 ng/ml. There was no significant difference between mean values for males and females at 24 h or between the means for those with acute or chronic renal failure ($P > 0.1$).

The mean V_{dapp} calculated by dividing the dose by the serum digoxin concentration at 24 h was 440 l or 6.7 l/kg (4.8–12.5 l/kg). Use of the 8 h value for serum digoxin concentration gave a mean V_{dapp} of 388 l or 5.9 l/kg. As the mean serum digoxin concentration at 24 h was only 0.2 ng/ml lower than the mean 8 h value, elimination during this period occurred at a very slow rate and a β phase may be assumed, with distribution to the tissues, complete by 8 h. The mean V_{dapp} calculated using theoretical zero-time values obtained by backplotting from the 24 and 8 h values in 15 patients was 370 l, or 6.5 l/kg (2.5–7.7 l/kg) and the mean $T_{1/2}$ 86 h.

We found no significant correlation between concentrations of serum sodium potassium, chloride,

creatinine, calcium, inorganic phosphorus, hematocrit, or age with the apparent volume of distribution calculated using either the 24 or 8 h values for serum digoxin concentration, or by backplotting to obtain theoretical zero-time values, expressed as l or l/kg ($P > 0.1$). Three correlation coefficients were found with marginal significance, considering the number of correlations performed: V_{dapp} expressed as l/kg and calculated using serum digoxin concentration at 24 h with ' CO_2 ' determined by autoanalyzer ($r = 0.49$, $n = 19$, $P < 0.05$) and V_{dapp} expressed as l/kg and calculated using theoretical zero-time values with serum albumin ($r = -0.56$, $n = 12$, $P < 0.05$) and also with total protein ($r = -0.64$, $n = 12$, $P < 0.05$). Average values and ranges were for ' CO_2 ' 18 mEq/l (11–24), albumin 3.5 g/100 ml (2.5–4.8) and total protein 6.3 g/100 ml (4.9–7.6).

No evidence of glycoside toxicity in terms of altered rhythm was recorded during the 24 h period under study, or subsequently in any of these patients, including four who were on a cardiac monitor in the intensive care unit for the first 24 h.

Discussion

Reports indicate patients with advanced renal failure have a reduced V_{dapp} for digoxin (Table 1), but with considerable variation in degree. The mean values of 440 l or 6.7 l/kg calculated from 24 h serum digoxin concentrations and of 370 l or 5.6 l/kg calculated

using theoretical zero-time values, confirm these reports. Our methods overestimate the true volume of distribution (Wagner & Northam, 1967), particularly the use of 24 h serum digoxin concentrations. Average values for V_{dapp} calculated from the literature were 555 l for 22 individuals with normal renal function (Bloom & Nelp, 1966; Gault, *et al.*, 1976; Koup, Greenblatt, Jusko, Smith & Koch-Weser, 1975; Shapiro, Narahara & Taubert, 1970), 350 l for 14 patients with renal failure but not on dialysis (Bloom & Nelp, 1966; Gault, *et al.*, 1976; Koup *et al.*, 1975; Marcus, Peterson, Sadel, Scully & Kapadia, 1966) and 378 l for 15 patients receiving hemodialysis, calculated in the inter-dialysis or pre-periods (Gault *et al.*, 1976; Koup *et al.*, 1975; Van der Vijgh & Oe, 1977). The methods used to calculate V_{dapp} however, varied.

The cause of the reduced V_{dapp} remains unknown. Factors which might contribute include decreased drug binding, decreased tissue mass, especially muscle but also red cell and kidney, acidosis, and hyperkalemia.

The protein binding of several drugs has been found to decrease with increasing renal failure (Reidenberg & Affrime, 1973). Koup *et al.* (1975) found that the binding of digoxin to plasma proteins was decreased in renal failure to 18% compared with 25% in healthy subjects, an observation which could represent a more general decrease in digoxin binding.

Van der Vijgh & Oe (1977) reported expansion of the volume of distribution of digoxin with dialysis, and also greater pre- and post-dialysis values with a larger surface dialyzer (1.5 m²) compared with use of a smaller dialyzer (1 m²). These findings suggest the presence of a dialyzable substance in renal failure which may influence the volume of distribution of digoxin, possibly by interfering with tissue binding and also could imply a relationship between the severity of renal failure and the extent of the reduction in the volume of distribution. There is however, inadequate data at different levels of renal function, to establish this relationship. Our finding of an inverse correlation between V_{dapp} and both albumin ($r = -0.56$) and total protein ($r = -0.64$) does not help explain the reduced V_{dapp} in renal failure.

Aronson & Grahame-Smith (1977) found an inverse correlation between V_{dapp} and age ($r = -0.75$, mean V_{dapp} 486 l or 7.4 l/kg and mean age 56 years) and suggested that this could be related to a change in the amount or activity of tissue sodium- and potassium- linked magnesium- dependent adenosine triphosphatase ($Na^+ - K^+ - ATPase$), in the sensitivity of that activity to inhibition by digoxin, as well as to a possible change in distribution of digoxin within other cell components. $Na^+ - K^+ - ATPase$ activity in human red cells has been found to decrease with age (Platt & Schoch, 1974) and also in some

Table 1 Apparent volume of distribution of digoxin with normal and abnormal renal function

Renal function	Ccr (ml/min)	$V_d^\dagger$	$V_d^{\dagger\dagger}$	n	Reference
Normal		510	480	6	Reuning <i>et al.</i> (1973)
					Shapiro <i>et al.</i> (1970)
	82-140	800	630	4	Bloom & Nelp (1966)
					Reuning (1973)
Renal failure	67-218		590	8	Koup <i>et al.</i> (1975)
	94-120		522	4	Gault <i>et al.</i> (1976)
	18-60		440	4	Gault <i>et al.</i> (1976)
	10-13	245	230	2	Marcus <i>et al.</i> (1966)
					Reuning <i>et al.</i> (1973)
	3-7		289	4	Koup <i>et al.</i> (1975)
	1-8	430	380	4	Bloom & Nelp (1966)
					Reuning <i>et al.</i> (1973)
Hemodialysis dependent					
Post-dialysis 1.5 m ² *	0-4	475		5	Van der Vijgh & Oe (1977)
Pre-dialysis 1.5 m ² *	0-4	384		5	Van der Vijgh & Oe (1977)
Post-dialysis 1.0 m ² *	0-2	366		3	Van der Vijgh & Oe (1977)
Pre-dialysis 1.0 m ² *	0-2	290		3	Van der Vijgh & Oe (1977)
Inter- or pre-dialysis	0		412	3	Koup <i>et al.</i> (1975)
Inter- or pre-dialysis	0-3		410	4	Gault <i>et al.</i> (1976)
Present study	0-4	370		22	

† Apparent volume of distribution after i.v. injection.

†† Apparent volume of distribution at steady state.

*Hemodialyzer area: 1.5 m² = Gambro Major. 1.0 m² = Gambro Nova.

patients with renal failure (Cole, 1973; Welt, Smith, Dunn, Czerwinski, Proctor, Cole, Balfe & Gitelman, 1967), possibly due to a dialyzable inhibitor (Cole, 1977). Loss of muscle mass with reduction in $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ and possibly other binding sites for digoxin, may occur with age and in some patients with renal failure. Although we did not find a correlation between age and V_{dapp} in this study where the mean age was 51 years, such a relationship could have been masked by a renal failure factor reducing V_{dapp} .

Autoanalyzer ' CO_2 ' also correlated ($r=0.49$, $P<0.05$) with V_{dapp} . However, the removal of one patient reduced the level of significance to $P=>0.05$. The method as used gives an estimate of CO_2 content. Acidosis may counteract the toxic effect of digitalis as a result of cellular influx of hydrogen ion and sodium and efflux of potassium (Bliss, Fishman & Smith, 1963; Schafer, Witham & Burns, 1960), a phenomenon which could be associated with reduced tissue binding of digoxin.

Coltart (1978) reported that hyperkalemia in dogs reduces the digoxin induced inhibition of $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ activity and also reduces total and microsomal-bound myocardial digoxin concentrations. Thus, increased serum potassium could be a factor contributing to the reduced V_{dapp} frequently found in renal failure. Two of the three patients reported by Aronson & Grahame-Smith (1976) with unexpectedly low values for V_{dapp} , high values for serum digoxin concentration and digoxin toxicity had hyperkalemia (7.0 and 6.6 mEq/l). We have observed in three dialysis dependent patients, sudden rises in serum digoxin of about 1 ng/ml from a level of 1.5–2 ng/ml in conjunction with sudden increases in serum potassium concentration from 5 to 7 mEq/l, and a rapid return of the serum digoxin to normal with return of the serum potassium to its previous level. Nevertheless we were unable to demonstrate any correlation between V_{dapp} and serum potassium in this study where the mean value was 5.0 and the range 3.8–6.8 mEq/l.

When evaluating an appropriate loading dose in renal failure, factors which might alter the sensitivity of the heart to digoxin must be considered, in addition to V_{dapp} . Aronson & Grahame-Smith (1976) reported three patients with renal failure and evidence of digoxin induced cardiac toxicity, but also noted that they found no previous comparable reports. Kramer *et al.* (1978) studied patients with serum digoxin concentrations > 2 ng/ml; 9% of those with values for serum creatinine > 3 mg/100 ml had evidence of toxicity, compared with 55% when the serum creatinine was < 1.5 mg/100 ml. They recommended a therapeutic range of 1.6 to 2.8 ng/ml for patients in renal failure and suggested that the

apparent increased tolerance could be due to the tendency to increased concentration of serum potassium, magnesium and hydrogen ion and to lower values for calcium in renal failure. We have prospectively followed 15 compliant patients on dialysis, usually 3 times a week, for 16 patient years (2–29 months). Maintenance digoxin dose was determined by a method previously described (Gault *et al.*, 1976) and adjusted when necessary to keep the serum digoxin concentration between 1 and 2 ng/ml. We used a 4 mEq/l potassium dialysate, determined the serum digoxin concentration on blood drawn before each dialysis and gave digoxin daily as the elixir, always after dialysis. The mean $\pm$ s.d. serum digoxin concentration for 1259 determinations was $1.26 \text{ ng/ml} \pm 0.42$. Of 48 values > 2 ng/ml in 11 patients, 44 were between 2.1 and 2.5 and 4 ranged from 2.6 to 2.8 ng/ml. The lack of clinical evidence of toxicity was unexpected, considering the frequency of toxicity reported for this range of serum digoxin concentrations (Doering & Konig, 1978; Gault *et al.*, 1976; Kramer *et al.*, 1978). These results and the usual fall in concentrations of potassium, magnesium and hydrogen ion and increase in ionized calcium during hemodialysis which might increase sensitivity to digoxin during dialysis, could be taken to support the view that there is increased tolerance to digoxin in advanced renal failure. Nevertheless, we suggest there is insufficient evidence to date to recommend an increase in the therapeutic range for digoxin in renal failure.

There is substantial evidence that the V_{dapp} of digoxin is reduced on average by about one third in advanced renal failure, but with wide variation from patient to patient and a possible increase towards normal with dialysis. Although there may be an increased tolerance to digoxin in renal failure (Kramer *et al.*, 1978) this could also vary considerably from patient to patient and from time to time in the same patient with variation in electrolyte, acid base and dialysis status. We suggest that an average i.v. loading dose of 10 $\mu\text{g/kg}$ is appropriate as this led to a mean $\pm$ s.d. serum digoxin concentration of $1.5 \text{ ng/ml} \pm 0.4$ at 24 h without toxicity. At times a lower dose might be used as in a patient with hypokalemia or obesity. The variable V_{dapp} and the possible presence of other factors which may influence toxicity in renal failure make assay of the serum digoxin concentration desirable when equilibrium has been attained after a loading dose, and during maintenance therapy.

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