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Clinical pharmacokinetics of digoxin in Nigerians

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Summary

The pharmacokinetics of digoxin have been studied in eight healthy volunteers, 23 congestive cardiac failure and 10 chronic renal failure patients. The mean serum digoxin concentrations in the volunteers and the congestive cardiac failure patients were significantly different ($P < 0.001$) from those in the chronic renal failure patients. The mean half-life of digoxin in the healthy volunteers (37.2 h ± 8.6 s.d.) was comparable to the widely accepted 40 h for digoxin half-life in normal individuals. Half-life was significantly prolonged in renal failure patients. There was a good inverse correlation, in the three groups, between serum creatinine and creatinine clearance, but the expected close correlation between the renal clearance of digoxin and serum creatinine was not demonstrated, probably because this was an oral study. There was no statistically significant difference in the age and weight in all three groups. There was also no significant difference in all parameters, measured and derived, between the volunteers and the congestive cardiac failure patients. However, when the volunteers and/or the congestive cardiac failure patients were compared with the renal failure patients, there was a significant difference in all parameters except age and weight. Thus, in the absence of renal impairment and hypokalaemia, standard dosages of digoxin can be used in congestive cardiac failure patients, provided symptoms and signs of toxicity are constantly monitored. Therapeutic drug monitoring of digoxin is desirable in view of its low toxicity : therapeutic ratio, and its kinetics should be studied in detail in each community to establish correct dosages to prevent and manage digoxin toxicity.

Résumé

On a étudié la pharmacocinétique de la digoxine chez huit volontaires en bonne santé, 23 malades souffrant d'insuffisance cardiaque congestive et 10 malades souffrant d'insuffisance rénale chronique. Les concentrations moyennes de sérum de digoxine chez les volontaires et chez les malades atteints d'insuffisance cardiaque congestive étaient nettement différentes ($P < 0.001$) de celles des malades souffrant d'insuffisance rénale chronique. La période moyenne d'administration de la digoxine chez les volontaires en bonne santé (37.2 h ± 8.6 s.d.) était comparable aux 40 h généralement acceptées pour la période d'administration de la digoxine chez les individus normaux. La période était nettement prolongée chez les malades souffrant d'insuffisance rénale. Il y avait une réelle corrélation inverse, dans les trois groupes, entre la créatinine sérique et l'élimination de la créatinine, mais la démonstration n'a pas été faite du rapport étroit et attendu entre l'élimination rénale de la digoxine et la créatinine sérique, probablement du fait qu'il s'agissait d'une étude orale. Il n'y avait pas de différence statistiquement significative en ce qui concerne l'âge et le poids de tous les individus des trois groupes. Il n'y avait pas non plus de différence significative en ce qui concerne tous les paramètres mesurés et dérivés entre les volontaires et les malades souffrant d'insuffisance cardiaque congestive. Cependant quand on a comparé les volontaires et/ou les malades souffrant d'insuffisance cardiaque congestive avec ceux atteints d'insuffisance rénale, il y avait une différence significative en ce qui concerne tous les paramètres, sauf l'âge et le poids. Ainsi donc, en l'absence d'affaiblissement rénal et d'hypokaliémie, des doses normales de digoxine peuvent être administrées à des malades souffrant d'insuffisance cardiaque congestive, à condition de contrôler constamment les symptômes et signes de toxicité. Le contrôle de la digoxine en tant que médicament thérapeutique est recommandé du fait

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du faible rapport toxique/thérapeutique, et sa cinétique devrait être étudiée en détail dans chaque communauté afin de déterminer les dosages corrects dans la prévention et la maîtrise de la toxicité de la digoxine.

Introduction

Digitalis has been used in the management of cardiac failure and cardiac arrhythmias for over two centuries but it is only since reliable and reproducible bioassay methods became available that detailed pharmacokinetic and pharmacodynamic studies on its components, mainly digoxin and digitoxin, have been possible. Assay methods now in common use include immunoassay — either radio or enzyme, ^{86}Rb uptake and ATPase inhibition. In clinical laboratories, the radioimmunoassay method introduced in 1969, and the related, competitive binding assay systems, are now widely used [1].

Digoxin has a low toxicity : therapeutic ratio and this is one of the main reasons why therapeutic drug monitoring of plasma digoxin levels is so widely undertaken. Factors that affect plasma digoxin concentrations have been studied extensively and reviewed [2]. They include renal impairment, electrolyte imbalance especially hypokalaemia, drug interactions, hypothyroidism and age. In old age, there is impaired renal function and a reduction in the apparent volume of distribution of digoxin. Hypokalaemia may reduce tubular secretion of digoxin, thus causing retention of digoxin. Tissue responsiveness to digoxin is also exaggerated. In thyroid disease, there are alterations in renal function and in the apparent volume of distribution of digoxin. Hypercalcaemia and probably hypomagnesaemia, hypoxia and acidosis increase tissue responses to digoxin while hyperkalaemia, hypocalcaemia, hyperthyroidism and young age (neonates) decrease tissue responses to digoxin. The presence of suspicion of any of the above would normally be an indication for the measurement of plasma digoxin concentrations. Criteria for routine plasma drug estimations have however been suggested [1,2]. These include a low toxicity : therapeutic ratio, a poor relationship between dose and plasma digoxin concentration, the presence of signs and symptoms of toxicity, which may be difficult to distinguish from those of the disease itself, and therapeutic effects, which may sometimes be difficult to measure.

Consequent on the above, measurement of plasma digoxin concentration may be of value in the diagnosis of toxicity or undertreatment, in overdosage, and in changing treatments in patients with renal impairment or on long-term therapy.

In a pilot study in Nigerians on chronic digoxin therapy for congestive cardiac failure, over 80% were found to be underdigitalized (digoxin level < 0.8 ng/ml) [3]. This was attributed to poor drug compliance as levels in in-patients were found to be within the therapeutic range. One patient in the study had a level > 3 ng/ml and symptoms and signs of toxicity, as well as biochemical evidence of renal failure. The present study was carried out to provide more information on the pharmacokinetics of digoxin in volunteers, congestive cardiac failure patients and advanced renal failure patients. The study was approved by the University College Hospital Ibadan Ethics Committee, but limited to oral dosing. Informed consent was given by all the subjects studied.

Patients and methods

The patients were consecutive new admissions to the Cardiac and Renal Units of the Department of Medicine, University College Hospital, Ibadan, Nigeria, who gave informed consent to participate in the study. Patients who were too ill and those who had taken digoxin prior to admission were excluded. Patients who deteriorated in the course of the study and/or needed rapid digitalization were taken off the study, while those who had measurable levels of digoxin in their initial blank plasma specimens were deleted from the data analysis. The volunteers were patients who had recovered from diseases other than cardiac or renal and whose renal function tests were normal.

All subjects had a clinical examination followed by biochemical and electrocardiographic investigations. A digoxin tablet (0.5 mg; Lanoxin, Wellcome) was administered at 08.00 h after an initial blank blood specimen, and 5-ml blood samples were taken at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72 and 96 h. The plasma was immediately separated and frozen at −21°C

until analysed. No further dose of digoxin was given throughout the period of blood collection. The subjects were examined clinically and electrocardiographically throughout the study period to detect those who needed more urgent digitalization. Most patients were on frusemide but none was on spironolactone or amiloride.

Drug assay

Plasma digoxin concentration was measured by radioimmunoassay using ^{125}I Digoxin RIA kits (Amertex Code IM 2031, supplied by Amersham, U.K.). Assays were done in duplicate and the mean value recorded.

Data analysis

The Kruskal-Wallis (one-way) analysis of variance was used for the comparison of all the three groups together — volunteers, congestive cardiac failure patients and chronic renal failure patients — while the Mann-Whitney *U*-test test was used for differences between one group and the others.

The half-life of digoxin was obtained from the equation:

$$t_{1/2} = \frac{0.693}{K_2},$$

where K_2 is the elimination constant.

Total digoxin clearance could not be calculated since there were no intravenous data, however, CL/F was obtained from the equation:

$$\frac{CL}{F} = \frac{Dose}{AUC},$$

where CL = clearance, AUC = area under the digoxin concentration–time curve, and F is the fraction of orally administered drug that reaches the systemic circulation.

The creatinine clearance was obtained from the equation [4]:

$$CL_{CR} = \frac{(140 - A) \times W}{72 \times S_{CR}},$$

where A = age, W = weight and S_{CR} = serum creatinine.

Values obtained for women were multiplied by 0.85 to account for the lower rate of creatinine formation.

Results

The mean group data are shown in Table 1. There were 21 males and 20 females, with an age range of 14 to 79 years. Table 2 shows the mean serum digoxin concentrations and these are depicted graphically in Fig. 1. There was a significant difference between the values obtained in the volunteers and chronic renal failure patients ($P < 0.001$) and between the

Table 1. Group data

Group	Age	Weight (kg)	Serum K^+ (mEq/l)	Serum albumin (g/100 ml)	Serum creatinine (mg/100 ml)	Blood urea (mg/100 ml)	Creatinine clearance (ml/min)
Volunteers ($n = 8$)	50.38 ± 11.44	56.1 ± 8.02	3.96 ± 0.374	3.58 ± 0.4	0.74 ± 0.11	26.13 ± 6.98	91.0 ± 11.1
Chronic renal failure ($n = 10$)	38.9 ± 20.05	56.06 ± 9.52	2.86 ± 0.158	2.83 ± 0.51	18.38 ± 12.32	241.7 ± 70.06	5.7 ± 3.05
Congestive cardiac failure ($n = 23$)	43.74 ± 13.74	59.3 ± 16.86	3.66 ± 0.37	3.34 ± 0.35	0.86 ± 0.21	29.09 ± 6.02	84.5 ± 23.43

Values are means ± standard deviation.

Table 2. Mean serum digoxin concentration (ng/ml)

Group	Time (h)										
	0.5	1	2	4	6	8	12	24	48	72	96	120
Volunteers (*n* = 8)	1.32 ± *0.37*	1.81 ± *0.52*	1.34 ± *0.56*	0.88 ± 0.46	0.60 ± 0.31	0.52 ± 0.26	0.47 ± 0.26	0.4 ± 0.24	0.28 ± 0.25	0.23 ± 0.15	0.15 ± 0.1	0.13 ± 0.05
Congestive cardiac failure (*n* = 10)	*1.01* ± 0.88	*1.48* ± 0.76	*1.55* ± 0.65	1.21 ± 0.64	0.95 ± 0.56	0.78 ± 0.42	0.68 ± 0.40	0.50 ± 0.31	0.42 ± 0.29	0.33 ± 0.26	0.27 ± 0.17	0.23 ± 0.17
Chronic renal failure (*n* = 23)	0.65 ± 1.1	1.5 ± 1.48	2.02 ± 1.35	2.18 ± 0.93	2.11 ± 0.84	2.02 ± 0.65	1.85 ± 0.56	1.42 ± 0.44	1.2 ± 0.41	0.97 ± 0.44	0.76 ± 0.34	0.63 ± 0.29

Values are means ± standard deviation.

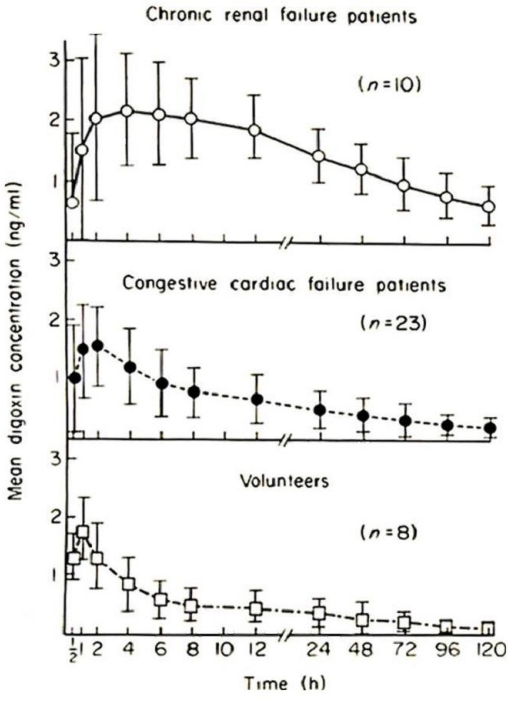

Fig. 1. Mean serum digoxin concentrations.

chronic renal failure patients and the congestive cardiac failure patients ($P < 0.001$). There was no difference ($P < 0.2$) between the volunteers and the congestive cardiac failure patients.

Table 3 shows a summary of individual pharmacokinetic data. There was no statistically significant difference in the age and weight in all three groups. All the other parameters measured showed some statistically significant difference among the groups ($P < 0.02$–$P < 0.001$) (Table 3). When each group was compared with the others, no significant difference was found between volunteers and CCF patients in all parameters measured. When volunteers and chronic renal failure patients were compared, there was a statistically significant difference in all but age and weight. When the cardiac failure patients were compared with the renal failure patients, there was also a statistically significant difference in all but age and weight (Table 4).

Discussion

The results obtained in this study were in general agreement with published data from similar studies in other parts of the world [1,5,6].

Table 3. Pharmacokinetic data

Group	Total AUC*	$t_{½}$†	C_{max}‡	t_{max} (h)§	CL/F (l/h)¶	CL/F (ml/min/kg)¶	Creatinine clearance
Volunteers ($n = 8$)	38.57 ± 24.9	37.2 ± 8.6	1.87 ± 0.51	1.19 ± 0.53	17.29 ± 8.86	5.38 ± 3.13	91.0 ± 11.1
Chronic renal failure ($n = 10$)	219.65 ± 100.2	80.95 ± 29.12	3.061 ± 1.11	3.6 ± 2.4	2.95 ± 1.82	0.9 ± 0.59	5.7 ± 3.05
Congestive cardiac failure ($n = 23$)	69.25 ± 63.12	56.96 ± 34.7	1.96 ± 0.74	1.65 ± 0.96	12.93 ± 8.7	3.87 ± 3.0	84.5 ± 23.43

Values are means ± standard deviation.
*AUC: Area under the curve.
†$t_{½}$: Half life.
‡C_{max}: Maximum concentration.
§t_{max}: Time to reach maximum concentration.
¶F: Fraction of an oral dose that is absorbed.

Table 4. Kruskal-Wallis test on all three groups

	Kruskal-Wallis	Mann-Whitney *U*-test†		
		A	B	C
AUC	*	*	NS	*
$t_{1/2}$	*	*	NS	*
C_{max}	*	*	NS	*
t_{max}	*	*	NS	*
CL (l/h)	*	*	NS	*
CL (ml/min/kg)	*	*	NS	*
Creatinine CL	NS	NS	NS	NS
Age (years)	NS	NS	NS	NS
Weight (kg)	*	*	NS	*
Serum K^+	*	*	NS	*
Serum albumin	*	*	NS	*
Serum creatinine	*	*	NS	*
Blood urea	*	*	NS	*

* = Significant difference, NS: not significant.
†A: Volunteers against chronic renal failure patients, B: volunteers against congestive cardiac failure patients, C: chronic renal failure patients against congestive cardiac failure patients.

Figure 1 shows that absorption of orally administered digoxin was good in all three groups, most rapid in the volunteers and least rapid in the chronic renal failure patients who, however, achieved the highest concentrations. Excretion was also most rapid in the volunteers and delayed in the chronic renal failure patients, with the congestive cardiac failure patients in an intermediate position, but much closer to the volunteers. There was no statistical difference between the volunteers and the cardiac failure patients. This is in keeping with the findings in similar studies, which stated that digoxin absorption is not reduced by cardiac failure to the extent that higher-than-usual doses should be administered therapeutic concentrations [7,8].

The mean half-life of digoxin in the volunteers (37.2 h) was comparable to the 40 h in Caucasians [6]. The half-life was markedly prolonged in the renal failure patients, with the congestive cardiac failure patients in an intermediate position. This would suggest a difference in the clearance or the apparent volume of distribution of digoxin, or both, in congestive cardiac failure. However, the result showed no statistical difference between the volunteers and congestive cardiac failure patients, both in the measured and derived data. Thus, in the absence of hypokalaemia and evidence of renal failure, standard doses of digoxin can be used in congestive cardiac failure patients, provided signs of toxicity are constantly being monitored. Some patients in renal failure develop congestive cardiac failure and vice versa. Such patients would require regular serum digoxin estimations and dose adjustments to forestall the development of toxicity.

The results showed a good inverse correlation between serum creatinine and creatinine clearance ($r = -0.76$ for volunteers, $r = -0.8$ for CRF patients and $r = -0.6$ for CCF patients) but the expected close correlation between the renal clearance of digoxin and serum creatinine was not demonstrated. Such correlation is, however, best shown by an intravenous study.

The results obtained in the chronic renal failure patients further emphasize the need for thorough renal evaluation of patients requiring digoxin, and the desirability of therapeutic drug monitoring of those on chronic digoxin therapy. Digoxin is excreted mainly through the kidneys and, in most patients, about 80% is excreted unchanged [6]. In 12% of patients, 20–55% is excreted as metabolites, mostly dihydroxydigoxin, which is relatively inactive. In a few subjects, other, more active, metabolites may be found in the urine. Renal elimination is mainly by glomerular filtration but some passive tubular reabsorption and active secretion occur. Elimination rate of digoxin is decreased at low diuresis, which suggests a low clearance in the elderly who generally have a low urine flow [9]. This is in accordance with the observed lack of correlation between creatinine clearance and serum digoxin in the elderly, whereas such a correlation has been found in younger people and has formed the basis of a formula for calculating the dosage regimen for digoxin.

Inter- and intraindividual variation (partly accounted for by age, weight and renal function), compliance, and drug interactions, especially with quinidine and drugs like diuretics, which deplete the body of potassium, are the other important factors that make serum digoxin concentration difficult to predict [10,11].

A detailed knowledge of the pharmacokinetics of digoxin has led to better dosage regi-

mens, prevention and better management of digoxin toxicity. As far as we know, this is the first study of digoxin pharmacokinetics in Nigerians and it is hoped that it will stimulate further similar, and more complex, studies on this most important and useful cardiac glycoside.

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