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Invited Review

Digoxin pharmacokinetic modelling – 10 years later

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Summary

A decade ago it was expected that pharmacokinetic models fitted to digoxin plasma and urine data would make a major contribution to its clinical use. In the interim, however, the results of many studies, involving modelling of digoxin data in disease states in both young and elderly patients and in interactions with other drugs, have not fulfilled this expectation.

Introduction

Ten years ago we published in the first edition of this journal, an article on the ' Pharmacokinetic profile of oral digoxin in healthy volunteers' (Collier et al., 1978). The study involved the fitting (non-linear least-squares fitting programmes) of blood and urine data simultaneously to both 3 and 4 exponential functions of the type ($Q_e^{-Kat} + A_e^{-\alpha t} + B_e^{-\beta t}$) and ($Q_e^{-Kat} + A_e^{-\alpha t} + B_e^{-\beta t} + C_e^{-\pi t}$). The results indicated that with oral dosing a classical two-compartment linear model gave the best fit to the data.

Ten years on we can ask ourselves a number of questions:

(1) Has a clearer picture emerged with regard to pharmacokinetic modelling of digoxin in health and disease?
(2) What are the clinical implications of pharmacokinetic analysis?
(3) Does the concurrent administration of increasing numbers of potent drugs affect the pharmacokinetic modelling of digoxin?

Pharmacokinetic modelling of digoxin 1978-1988

A 'MEDLINE' search of the literature using the key words 'digoxin' and 'pharmacokinetics' indicated that 127 papers were published during this time; 8 of the papers were reviews (Appendix 1). If the term 'models–theoretical' was included in the literature search, the number of articles was 9 (Appendix 2); if 'models' was used alone, the number of articles was 8 (Appendix 3). The original article (Collier et al., 1978) was not cited.

In the original paper we discussed how the results of our digoxin pharmacokinetic modelling compared with previous studies. Using tritiated drug i.v., Reuning et al. (1973) demonstrated that the best fit to the data was represented by a 2-compartment model, agreeing with our results; whereas Doherty and Perkins (1962), Doherty et al. (1967), Kramer et al. (1973) and Sumner et al.

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(1976) presented evidence to suggest a 3-compartment model. We suggested that the discrepancy between our results and the 3-compartment group was that with oral absorption, K_a is probably a hybrid constant that defines both the absorption and initial phase of rapid distribution of digoxin.

Digoxin pharmacokinetic modelling has been investigated in health and disease, and in young (low-birth weight, premature and normal delivery infants) and elderly patients. However, most reviewers quoted earlier studies that they or others had undertaken.

Iisalo in 1977 stated in his review that the time course of the serum digoxin concentration after an i.v. injection or infusion indicates that the pharmacokinetics of digoxin should be described by a model containing at least two kinetically distinct compartments. He quoted Dengler et al. (1973), Doherty (1968), Greenblatt et al. (1974), Reuning et al. (1973) and Nyberg et al. (1974); he also commented that a 3-compartmental analysis has been preferred by Kramer et al. (1973) and by Sumner et al. (1976). Aronson (1980), discussing digoxin plasma concentration in hypothyroid and euthynoid patients stated that Shenfield et al. (1977) did find a lowered apparent V_d of the central compartment of a 2-compartment model in patients with hypothyroidism. Lawrence et al. (1977) noted a similar trend, but this was associated with two peripheral compartments of a 3-compartment model. A recent review (Mooradian, 1988), referring to work by Schenk-Gustafsson et al. (1981), states that the distribution of digoxin is best represented by a 3-compartment model with the slow distribution phase accounting for the lag time between the inotropic effects and the plasma concentration profile.

Studies in infants (Wettrell and Andersson, 1977), indicated that i.v. digoxin was best represented by a 2-compartment model (Dungan et al., 1972; Morselli et al., 1975; Wettrell, 1976). In premature infants Hastreiter et al. (1982) fitted models to the data following i.v. digoxin (2 μg/kg) administration and demonstrated improved fitting to the data in 5/6 infants with a 3-compartment model. However, to compare their results with others (Nyberg et al., 1974; Morselli et al., 1975; Wettrell, 1977), they used the parameters from the 2-compartment model fitting. The pharmacokinetic profile of digoxin was evaluated in infants with low birth weight (Collins-Nakai et al., 1982); following rapid i.v. injection, the 24-h serum digoxin level data of each infant were best described by a 2-compartment model. This is in agreement with a previous study in infants with low birth weight (Warburton et al., 1980).

Clinical implications of pharmacokinetic analysis

Sumner et al. (1976) stated that 'it is not possible to match compartments (in their case a 3-compartment model) with exact tissue spaces. The reasons for introducing compartments to represent body tissues is not simply to fit the data but to obtain the time-course of drug concentration at the site of action viz. receptors in the myocardium'. The amount of drug in compartments must be correlated with observable pharmacodynamic effects, e.g. Reuning et al. (1973), using a 2-compartment model, suggested that digoxin in the tissue compartment peaked at 5 h; this correlated with changes in electromechanical systole (QS_2) and left ventricular ejection time (LVET) (Weissler et al., 1972). Similar results were also shown with deslanoside C and changes in QS_2 (Weissler et al., 1966) and digoxin and LVET (Hoeschen and Cuddy, 1975). Haemodynamic confirmation was also provided by Davidson and Gibson (1973) who demonstrated that the inotropic effects were not related to plasma levels but rather to predicted tissue concentration changes. It is interesting that Sumner et al. (1976) with their 3-compartment model quote peak tissue values of 1–2 h (compartment 2) and 8–12 h (compartment 3). They commented that the S.D. of parameters ranged from 4 to 74% (study in 4 healthy volunteers); and state 'this illustrates the difficulty of drawing quantitative conclusions from the rate constants obtained from multi-compartmental models'. These differences in pharmacokinetic parameters with different models were also highlighted by Hastreiter et al. (1982) (Table 1). Comparing the 2- and 3-compartment models, $t_{\frac{1}{2}}$ (h) increased by 47.7%, AUC (ng/ml/h) by 28.5%, V_{d_β} (liter/kg) by 13%, $V_{d_{ss}}$ (liter/kg) by 13.5% and Cl (ml/min/kg) decreased by 20.9% as did V_c (liter/kg) by 6.5%. The

TABLE 1

Comparison of pharmacokinetic parameters of digoxin in premature infants calculated using 2- and 3-exponential models

Parameter	2 EXM (mean ± S.E.M.)	3 EXM (mean ± S.E.M.)
$T_{1/2}$ (h^{-1})	45.5 ± 7.3	67.2 ± 6.9
AUC (ng/ml/h)	262.9 ± 23.6	337.7 ± 37.5
V_c (liter/kg)	0.62 ± 0.10	0.58 ± 0.10
$V_{d\beta}$ (liter/kg)	5.37 ± 1.00	6.17 ± 0.95
V_{dss} (liter/kg)	4.95 ± 0.96	5.72 ± 0.90
Cl (ml/min/kg)	1.34 ± 0.24	1.06 ± 0.15

EXM, exponential model; SEM, standard error of the mean. Data from Hastreiter et al., 1982.

authors state that these differences including the change in $t_{\frac{1}{2}}$ from 45.7 ± 7.3 to 67.2 ± 6.7 h (mean ± S.E.M., $n = 6$) were not significant. When they compared their 2-compartment model data in premature infants with data of different age groups (Nyberg et al., 1974; Morselli et al., 1975; Wettrell and Andersson, 1977), i.e. premature, neonate, infant, child and adult, they found no differences in the kinetic parameters for $t_{\frac{1}{2}}$, V_d and Cl for the premature infants but observed differences between other different age groups.

This highlights one of the advantages of modelling in that different age groups will handle digoxin differently and if this is not taken into account, toxicity could follow. However, it does indicate that 'like with like' models must be compared, e.g. in this case 2-compartment, although in the Hastreiter et al. (1982) study a 3-compartment model gave the best fit to the data.

The variability in digoxin pharmacokinetic

TABLE 2

Some pharmacokinetic data on digoxin

Author	n	α (h^{-1})	$t_{1/2\alpha}$ (h^{-1})	β (h^{-1})	$t_{1/2\beta}$ (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{el} (h^{-1})	V_{dc} (liter/kg)	V_{dss} (liter/kg)	$V_{d\beta}$ (liter/kg)
Healthy subjects											
Koup et al., 1975		1.99		0.017	44.1					8.1 [1]	
Kramer et al., 1974											
(2-compartment)					26				0.76		
(3-compartment)					45				0.60		
Nyberg et al., 1974	5	1.33	0.52	0.020	34.65	1.02	0.15	0.18	0.78	5.95	6.80
Reuning et al., 1973	14			0.020		0.56 [2]	0.15 [2]	0.08 [2]	1.1	5.1	
Ritschel, 1976				0.017	40.8				0.37		
Sumner et al., 1976 (3-compartment)	4								0.53		
Patients											
Koup et al., 1976 (renal failure)	5	1.21	0.57	0.009	79.2					4.44	4.72
Ohnhaus et al., 1974 (renal failure)	33			0.006	110.0				0.51		
Rabkin and Grupp, 1975 (heart failure)	6	1.42	0.58	0.017	48.38	1.004	0.114	0.188	0.58	5.0	
Reuning et al., 1973 (renal insufficiency)	7				103	0.45 [2]	0.11 [2]	0.04 [2]	0.73	3.3	
Wettrell, 1976 (infants from 2 to 81 days, heart failure)	7	1.36	0.52	0.029	29.8	0.974	0.15	0.27	1.3	9.9	12.1

Data from Iisalo (1977).

α and β, the slopes of distribution and elimination phase respectively (on a schematic graph of serum concentrations plotted logarithmic scale); $t_{1/2\alpha}$ and $t_{1/2\beta}$, half lives of the distribution and elimination phase respectively; k_{12} and k_{21}, rate constants associated with drug transfer from central to the peripheral compartment and vice versa; k_{el}, rate constant elimination; V_{dc}, volume of central compartment; V_{dss}, distribution volume at steady state; $V_{d\beta}$, distribution volume during the elimination phase.

[1] Calculation based on the patients' weights indicated by the authors.

[2] Means of the values referred by the authors from other published data.

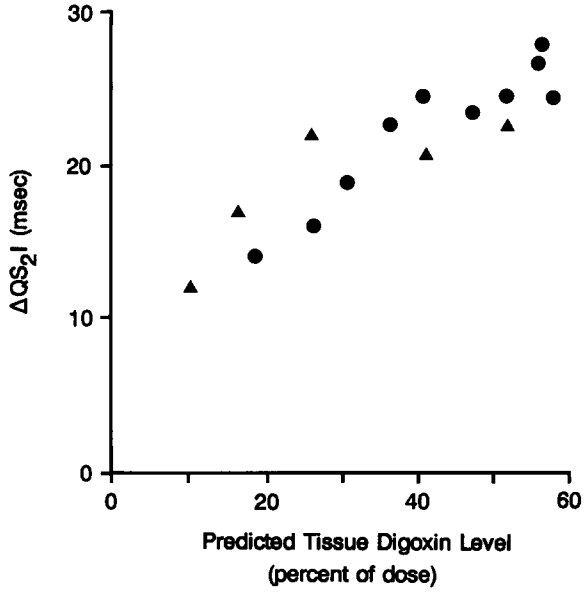

Fig. 1. Plot of the averaged ΔQS_2I data vs the tissue digoxin level predicted for compartment 2 from the fit to the serum concentration–time data only. Points on the onset portion of the ΔQS_2I time curve are shown as (●) and those on the decay portion as (▲) (data from Kramer et al., 1979).

parameters depending on which type of model was fitted to the data and whether the studies were carried out in healthy volunteers or patients, is further demonstrated in Table 2. Plasma elimination half-lives varied from 26 to 45 h in healthy volunteers, depending on the pharmacokinetic model, and from 79 to 110 h in patients with renal failure and 48.4 h in patients with heart failure. Kramer et al. (1979) designed a study to demonstrate the relationship between the pharmacokinetics and pharmacological effects of digoxin using serum digoxin and systolic time intervals in 12 normal males following a 1.0 mg i.v. bolus. The results of this study indicated that the serum/time profile was best represented by a 3-compartment model; the levels of digoxin in the 'deep' compartment were closely related to the intensity of response as measured by the ΔQS_2I (change in electromechanical systole corrected for heart rate which is inversely proportional to a direct invasive quantitation of inotropy) (Fig. 1). The time to reach peak digoxin tissue level was 5 h (3–8 h), consistent with the intensity of digoxin effects in the tissue compartment; a similar hemodynamic response time of 4–8 h was described by Ochs et al. (1980).

However, despite the relationship between pharmacokinetic parameters obtained following modelling and dynamics, Kramer et al. (1979) suggested that further substantiation of their validity is required with regard to the variability inherent in the response measurement both intersubject and intrasubject; this leads to the relationship being valid only for the averaged data but not for any individual in their study. Secondly, the limited range of the changes on ΔQS_2I coupled with the intersubject variability makes it difficult even for averaged data to distinguish between different possible mathematical relationships between drug level and response. They suggest that improvement should be related to a more reproducible response measurement for digoxin, with further confirmation for the relationship between ΔQS_2I and the degree of inotropy, and thirdly, they question the specificity of the digoxin radioimmunoassay.

Effects of other drugs on the pharmacokinetics of digoxin

Mooradian (1988) recently summarized the effects of other drugs on the pharmacokinetics of digoxin (Table 3) with regard to effects on absorption, protein binding, metabolism and excretion. Also included was a list of drugs which increase serum digoxin concentrations by unknown mechanisms, e.g. the antiarrhythmics; amiodarone, flecainide and propafenone and many of the newer calcium antagonists.

De Vito and Friedman (1986) reported rises of 70% in serum digoxin concentration with verapamil, 40% with nifedipine and 33% with diltiazem. However, despite the evidence that increased serum digoxin concentrations can lead to increased inotropic effects, few patients have experienced an increase in adverse effects. These authors suggest that changing digoxin dosage prior to initiating calcium antagonist therapy is not justifiable. Marcus (1985) stated that 'although there has been a tremendous increase in our knowledge of drug interactions with digitalis, most of the studies

TABLE 3

Agents affecting the pharmacokinetics of digitalis

Alteration	Agents
Decreased absorption	Activated charcoal, antacids, cholestyramine, colestipol, cytotoxic agents [cyclophosphamide, doxorubicin (adriamycin)], dietary fibre, kaolin-pectin, metoclopramide, neomycin, sulphasalazine
Increased absorption	Antibiotics (by inhibiting gut flora), anticholinergics (propantheline)
Inhibition of serum protein binding	Clofibrate, phenobarbitone, phenylbutazone, prazosin, sulphonamides, tolbutamide, warfarin
Enhanced hepatic metabolism	Phenobarbitone, phenylbutazone, phenytoin, rifampicin (rifampin)
Enhanced renal excretion	Hydralazine, levodopa, nitroprusside
Inhibition of renal tubular secretion	Quinidine, spironolactone, triamterene, trimethoprim, verapamil
Inhibition of extrarenal clearance	Diltiazem, quinidine, verapamil
Decreased volume of distribution	Quinidine
Increased serum digoxin concentrations (mechanism unknown)	Amiodarone, aspirin, bepridil, diltiazem, flecainide, ibuprofen, indomethacin, nifedipine, nicardipine, nisoldipine, nitrendipine, propafenone

Data from Mooradian (1988).

included relatively few patients and were not designed to examine drug interaction at steady state in cardiac patients.

The effects of other drugs on digoxin pharmacokinetic models is not reviewed.

Conclusion

The debate on the pharmacokinetic modelling of digoxin continues as to whether the data are best represented by a 2- or 3-compartment model. Great disparity in pharmacokinetic parameters occur (Tables 1 and 2) depending on the model chosen. Also, no clear picture emerges of the relationship between the pharmacokinetic compartments and haemodynamic response. Obviously differences will occur in the way in which digoxin is handled by the body, depending on the age of the patient, disease state, renal function, patient compliance and administration of other drugs. However, Wagner (1974) found only 34% of the variability in digoxin plasma concentration in 25 patients was due to age, height, dose, body weight and renal function. Similar results were demonstrated by Peck et al. (1973) and Aronson et al. (1978). Furthermore, Aronson (1980) questions the reliability of digoxin nomograms which are based on average values of pharmacokinetic variables of a population rather than the individual patient. Hastreiter et al. (1982) concluded their study by saying that 'the use of computers for the management of premature infants given digoxin *is not advocated*. The simple use of serum digoxin assay levels constitute a most useful tool in management ... in addition to a knowledge of the concepts of immaturity of renal function, low volume of distribution and clearance, alterations in protein binding, tissue sensitivity and metabolism, plus a knowledge of the infant's changing status'. Mooradian and Wynn (1987), who evaluated the usefulness of pharmacokinetic predictions of serum digoxin concentrations in the elderly, stated that further studies were needed to improve the pharmacokinetic prediction of digoxin dosage regimens and that frequent monitoring of serum digoxin concentrations along with maintaining normal concentrations of serum electrolytes remain the only reliable practice for reducing the incidence of digoxin toxic reactions in the elderly. These comments, together with those of Kramer et al. (1979) mentioned earlier, indicate that our understanding of pharmacokinetic modelling of digoxin and its clinical implications may not have progressed much in 10 years.

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