Pharmacokinetics of Cardiovascular, Central Nervous System, and Antimicrobial Drugs

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Introduction

During the last 20 years the drug industry and the practice of medicine have expanded at an incredible rate. This has been due to the combined influences of a number of factors, including rapid advances in pharmacology and pathology, and accompanying advances in such diverse areas as pharmacodynamics, pharmacokinetics, and the development of sophisticated drug delivery systems. The last of these has been the focus of frenzied activity during the last ten years, and is likely to continue for some time. More recent advances in immunopharmacology and the use of monoclonal antibodies have provided further impetus to the quest for new drugs in many therapeutic areas.

As the number, selectivity, and potency of therapeutic agents have increased, so has the need to understand more precisely how these agents are handled by the body and what influence this has on their therapeutic efficacy. The recent rapid expansion of the drug industry, and the need to understand and hopefully regulate various aspects of drug absorption, distribution, metabolism, and excretion (ADME) have provided the perfect spawning ground for the disciplines of pharmacokinetics and biopharmaceutics.

At all levels of drug use, from industrial or academic development laboratories, to the daily practice of medicine, and to regulatory practices world-wide, it is recognized that in order to develop, understand, and use a drug with optimum benefit to the patient the multifactorial, qualitative and quantitative aspects of its ADME characteristics must be clearly understood.

During the ten years from 1970 to 1979 one of us (PGW) had the opportunity to prepare a series of review articles for the Chemical

Society, later the Royal Society of Chemistry, on the subject of drug kinetics.[1-5] Each of these review articles covered a two year period and provided a broad, but necessarily not exhaustive, coverage of pharmacokinetic and biopharmaceutic literature for many therapeutic drug classes.

This exercise was rewarding for the writer, and hopefully also for the reader, in providing a continuous update in this rapidly developing and changing area of research. On completion of the reviews it appeared logical to compile them into one text so as to provide a comprehensive review of the subject during one decade.

Space does not permit this to be done for all drug classes. Therefore, in order to provide maximum coverage and also to limit this book to a reasonable size, three major drug classes were selected, cardiovascular agents, drugs acting on the central nervous system (c.n.s.), and antimicrobial agents. These three classes are clearly unrelated to each other, but nonetheless represent three major therapeutic areas that have undergone dramatic changes during recent years.

Owing to the time that has elapsed since completion of the last review, covering the period 1978-79, coverage in this book has been exanded by three additional years to include a total period of 13 years, from 1970 through 1982.

The book is thus divided into three major sections, each being devoted to a single drug class. Specific drug groups within each class are indicated by separate subheadings. As in the original reviews, each drug, or group of drugs when they are considered together, will be discussed in the order of absorption, distribution, metabolism, and excretion, provided information is available. Within each of these sections information is presented in the approximate order in which it appeared in the literature.

Because of the huge volume of literature that has been generated on the pharmacokinetics of cardiovascular, central nervous system,

and antimicrobial agents, no attempt has been made to provide an exhaustive coverage of the literature. Such information can be obtained from computerized searches. Rather, we have attempted, by selective reviewing, to describe the trends that have occurred in pharmacokinetic and biopharmaceutic studies for three major drug classes during a large segment of the relatively short history of this important and ever-changing subject.

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1 Cardiovascular Drugs

Cardiac Glycosides and Other Cardiotonic Agents

Digoxin

The perennial problem of digoxin toxicity associated with its narrow therapeutic index and variable p.o. bioavailability, and also the advent of the radioimmunoassay, have given rise to a large number of studies concerning digoxin absorption,[1-7] relationships between bioavailability and *in vitro* dissolution profiles,[8-14] tablet disintegration,[15] and the influence of particle size on digoxin bioavailability.[16,17]

Some studies have indicated only small differences,[18-20] while others have indicated larger differences[21-23] in digoxin availability from oral dosage forms. Digoxin absorption is generally[24-27] but not always[28] superior from a solution or elixir compared to tablets, and absorption from both solid and solution dosage forms is not markedly affected by accompanying food.[29]

Differences in digoxin availability from solid dosage forms can be quite large. A study on four commercial products available in the United States yielded a seven-fold difference in serum digoxin levels between two of the products with other brands giving intermediate values.[30] The product yielding lowest serum levels did not comply with United States Pharmacopeia specifications for potency.[31,32] It has been suggested that blood levels alone may give erroneous bioavailability data for digoxin and should be supplemented by cumulative urinary excretion studies.[33]

Several studies have reported superior absorption of digoxin from solutions contained in capsules compared with tablet formulations or

conventional solutions.[34-36] In one of these studies the intriguing observation was made that urinary excretion of digoxin following a 3 h i.v. infusion was 21% greater than that following a 1 h infusion of the same quantity of drug.[35] This inexplicable phenomenon has implications for the use of digoxin injections as primary standards in bioavailability testing.

The superior availability of digoxin from an encapsulated solution compared with tablets and solutions has been demonstrated also when doses are given following a substantially high-fat meal.[37] Mean serum digoxin levels obtained in 12 individuals are shown in Figure 1.1. Following a single 0.4 mg dose, capsules produced peak serum digoxin levels of 2.7 ng ml^{-1} at 50 min compared with 1.6 ng ml^{-1} at 68 min from tablets, and 1.6 ng ml^{-1} at 73 min from a solution. Faster absorption of digoxin was obtained from a digoxin-hydroquinone complex, compared with conventional tablets in man,[38] whereas digoxin absorption was inhibited in subjects who were receiving sulphasalazine,[39] and also in patients with progressive systemic sclerosis.[40]

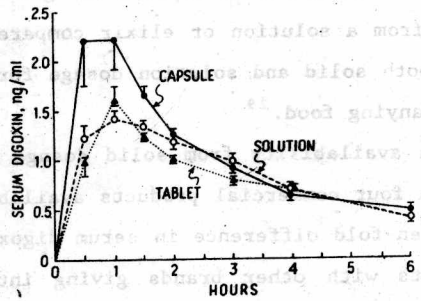

Figure 1.1 Mean serum digoxin concentrations in twelve normal subjects 0 to 6 h after administration of 0.4 mg of each of three digoxin formulations (capsule, solution, or tablet) following a high-fat meal. Bars indicate 1 SEM. (Reproduced by permission from Clin. Pharmacol. Ther., 1977, 21, 278)

Apart from product[41,42] variations, the absorption of orally administered digoxin may be influenced also by other drugs,[43] antacids or antidiarrheal agents,[44-46] and by drugs affecting biliary excre-

tion of gastric motility,[47-49] although the latter effect may occur only with slowly dissolving formulations.[50]

Other studies using solubilized ^{3}H-digoxin show that digoxin absorption is not greatly affected by gastric ulcers.[51] When the drug is dosed as a solution, 40-60% is absorbed from the stomach and the proximal small intestine.

In examining the influence of a kaolin-pectin suspension on digoxin absorption, Albert et al.[52] calculated digoxin relative bioavailability assuming constant nonrenal drug clearance as in equation 1.1:

$$\frac{F^t}{F^s} = \frac{AUC^{\infty,t}}{AUC^{\infty,s}} - \frac{AUC^{\infty,t}}{D^t}\,(Cl_R^s - Cl_R^t) \qquad (1.1)$$

nonrenal clearance varying in proportion to renal clearance, as in equation 1.2:

$$\frac{F^t}{F^s} = \frac{AUC^{\infty,t}}{AUC^{\infty,s}}\left(\frac{Cl_R^t}{Cl_R^s}\right) \qquad (1.2)$$

and constant plasma clearance, as in equation 1.3:

$$\frac{F^t}{F^s} = \frac{AUC^{\infty,t}}{AUC^{\infty,s}} \qquad (1.3)$$

In the equations, F^t/F^s is the bioavailability ratio of the test (kaolin-pectin) and standard treatments, AUC^{∞} is the area under the plasma concentration-time curve through infinity, and Cl_R is the renal clearance. Application of equations 1.1, 1.2, and 1.3 yielded respectively bioavailability ratios of 0.82, 0.86, and 0.84 when kaolin-pectin was administered 2 h before digoxin, and 0.95, 1.0, and 0.90 when kaolin-pectin was given 2 h after digoxin, indicating only slight drug interactions. However, when the kaolin-pectin and digoxin were given together, the mean digoxin bioavailability was reduced to 0.4. Although a slower absorption rate of digoxin may have a marked effect on plasma levels of drug shortly after a single dose, this effect is attenuated with repeated dosing due to the long biological $t_{0.5}$ of digoxin.

Large intersubject variations in serum digoxin concentration profiles, due to erratic absorption or distribution, have been observed in patients suffering from congestive heart failure.[53,54] The erratic bioavailability could also be due to a varying degree of digoxin degradation in the stomach as a function of gastric pH. Gault et al.[55] reported that 90 min after administration of ^{3}H-digoxin with maximum acid secretion stimulated by pentagastrin, nearly all of the radioactivity remaining in the stomach was present as hydrolysis products, mainly digoxigenin. Gastric acid stimulation also resulted in a marked increase in urinary metabolites in the same subjects.[56] However, a recent study in which ten healthy volunteers received 0.75 mg digoxin tablets confirmed that food ingestion had no effect on the absorption of the unchanged glycoside.[57]

Double peaks that have been reported in digoxin plasma levels after p.o. doses[58] may be due to absorption of dihydrodigoxin formed by bacteria in the lower intestine.[59] Similar observations of double peaks in circulating lanatoside C after p.o. doses have been attributed to bacterial metabolism of the relatively poorly absorbed lanatoside C to the more readily absorbed digoxin.[60-61] This acid-catalysed conversion is reduced in the presence of antacids.[62] Low recovery of ^{3}H-digoxin and its metabolites in the lymph of patients undergoing thoracic duct drainage indicates the lymphatic channels provide a minor pathway for digoxin absorption.[63]

The distribution space of digoxin in man, from the relationship $V\beta = \text{Dose}/\beta \cdot \int_0^\infty C$ appropriate to the two-compartment model, is ca. 5.3 l kg^{-1} whereas for lanatoside C is 4.4 l kg^{-1}.[64] The distribution space for digoxin decreases in patients with renal failure, and this may be attributed either to a decrease in the volume of extracellular fluid or to a decrease in the extent of drug-tissue binding.[65]

Accumulation of digoxin and ouabain in the mouse liver is reduced by probenecid, leading to considerable redistribution of drug in the body.[66] The mechanistic basis of this probenecid-digoxin interaction

is not known. Approximately 30% of circulating digoxin is bound to human serum albumin over the concentration range 0.02 - 14.8 ng ml^{-1}.[67] The number of binding sites is almost infinite, but the binding constant is extremely small with a value of 6.8×10^{-4} mol^{-1}. Extensions of earlier studies have shown that a good correlation exists between the positive inotropic effect of digoxin and the amount of drug bound loosely to cardiac microsomal cell fractions. Tightly bound drug did not correlate well with positive inotrophy.[68]

Several studies have correlated blood digitalis levels with therapeutic[69-71] and toxic[72,73] effects. However, toxic reactions from low serum digitalis levels, nontoxic reactions from high serum levels[74] and myocardial resistance to high serum levels have been reported.[75]

Schoenwald[76] has described a relationship between ventricular heart-rate slowing and circulating digoxin levels, and has used this relationship to demonstrate prolonged digoxin absorption over 120 h after p.o. doses. This prolonged and fluctuating absorption suggests that enterohepatic cycling of digoxin in man may be extensive. Circulating levels of digoxin after rapid i.v. injection into human volunteers have been described using a three-compartment model.[77] However, comparison of three- and two-compartment model analyses shows that the disposition rate constants for the second compartment are similar for both models and that the equivalent rate constants for the third compartment of the three-compartment model are extremely high relative to other rate constants. Thus, the third compartment is relatively "shallow" and would not be detected after any other form of digoxin dosage. The "gamma" phase elimination $t_{0.5}$ reported in this study is numerically similar to "beta" phase $t_{0.5}$ generally obtained from two-compartment analysis.[78-80]

A physiological pharmacokinetic model, designed to describe the time curves of plasma and tissue concentrations of digoxin in the dog, was adapted with partial success for use in humans by considering

species differences in organ volume and flow rates.[81] The model adequately predicted digoxin levels in patients with moderate uraemia but provided a relatively poor fit in anuric individuals. Preferential uptake of digoxin by particular tissues is demonstrated by reports of a mean myocardial tissue:serum digoxin level ratio of 67 in patients undergoing heart surgery[82] and mean c.s.f:serum digoxin level ratio of 0.3 in infants and in adults receiving digoxin therapy.[83]

Aronson et al.[84,85] investigated the use of digoxin inhibition of ^{86}Rb uptake by human erythrocytes to monitor pharmacodynamic effects of this drug. Good correlations were obtained between distribution characteristics of digoxin and the therapeutic response of patients with atrial fibrillation to changes in erythrocyte ^{86}Rb uptake. The tendency for oral digoxin to induce cardiac dysrhythmia has been shown in dogs to be unrelated to the occurrence of transient peak circulating levels of drug.[86]

Circulating levels of digoxin in man are increased by the presence of quinidine,[87] but are decreased by penicillamine.[88] Increased glycoside levels in the presence of quinidine appear to be associated with displacement of digoxin from tissue binding sites. The decreased glycoside levels due to penicillamine appear also to be due to a redistribution phenomenon as neither the digoxin absorption nor the elimination rate are affected by penicillamine.

Penetration of digoxin into the c.n.s. is poor, and the ratio of c.s.f.:serum levels in patients is 0.14.[89] Even within the brain the distribution of digoxin is variable, as levels in the choroid plexus far exceed those in cerebral grey and white matter. The choroid plexus binds digoxin to an extent similar to the myocardium.[90]

The inotropic effect of digoxin, as measured by changes in the QS_2 index (ΔQS_2I) is closely related to calculated digoxin levels in the slowly distributing (deep) tissue compartment of the kinetic three-compartment model, although it is uncertain whether this is a linear or nonlinear relationship.[91]

The distribution of digoxin into the skeletal muscle, which is affected by cardiac glycosides similarly to the heart,[92] has been examined.[93,94] In healthy subjects receiving 0.13-0.5 mg d^{-1} digoxin, a significant correlation existed between the digoxin concentrations in serum and skeletal muscle (Figure 1.2) as well as between skeletal muscle digoxin concentration and cardiac effect, measured by changes in QS_2I.[93] The estimated half-life of digoxin in skeletal muscle, ca. 2 d, was comparable to that reported for serum digoxin. A similar study conducted in patients during digitalization or during withdrawal of digoxin treatment showed similar, albeit statistically insignificant, correlations between changes in systolic time intervals and steady-state serum or skeletal muscle digoxin concentrations.[94] Bonelli et al.[95] investigated the distribution of digoxin into cerebrospinal fluid (c.s.f.) after 9 d of treatment with β-methyldigoxin or β-acetyldigoxin. Equipotent doses of the two compounds gave rise to similar plasma:c.s.f. digoxin concentration ratios of approximately 3.5:1.

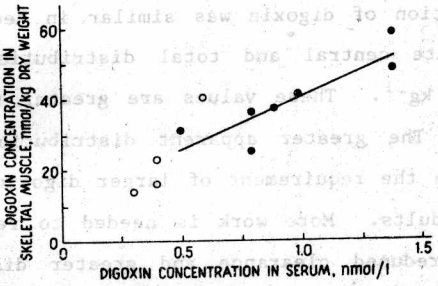

Figure 1.2 Correlation between digoxin concentration in serum and skeletal muscle at the higher dose level ($r = 0.87$; $p < 0.05$; $n = 7$). For comparison data from four subjects at the lower dose level are shown (o). Reproduced by permission from Eur. J. Clin. Pharmacol., 1981, 19, 89.

Critical analysis of previous work regarding the distribution of digoxin in hyperthyroid patients showed that, contrary to original suggestions, digoxin distribution was similar in normal subjects and hyperthyroid patients, while both renal and nonrenal clearance increased substantially in hyperthyroidism.[96]

It is well established that therapeutic doses of digoxin are higher in infants than in adults. Although the underlying reason for higher dose requirement in infants is uncertain, it appears to have a pharmacological rather than a pharmacokinetic basis. Different studies have shown that therapeutic serum digoxin levels are also higher in infants than in adults,[97] while absorption,[98] protein binding,[99] and elimination characteristics[100] are similar in the two populations. However, in neonates at full-term high circulating digoxin levels may be associated with low renal elimination of glycoside.[101] Therapeutic doses, and also serum levels of digitoxin, are similarly higher in infants than in adults.[102]

Changes in dose-response relationships for digoxin after corrective heart surgery may be related to changing haemodynamic status in neonates, infants, and children.[103] Renal clearances of digoxin were lower and elimination $t_{0.5}$ values were longer in neonates compared with infants, and renal clearance in both neonates and infants was approximately two-fold greater than creatinine clearances.[104] Distribution of digoxin was similar in neonates and infants, with steady-state central and total distribution volumes averaging 1.3 and 9.9 l kg^{-1}. These values are greater than those reported in adults.[105] The greater apparent distribution volumes reported here may explain the requirement of larger digoxin doses by children compared with adults. More work is needed to resolve the opposing influences of reduced clearance and greater distribution volumes of digoxin on circulating digoxin levels and the greater tolerance to digoxin by infants compared with adults.

Digoxin clearance increases rapidly during the first three months of life, apparently due to development of both renal filtration and tubular secretion processes.[106] Although neonates and very young infants have a high digoxin tolerance, impaired clearance of drug in these populations suggests that some recommended doses, particulary in neonates, may be too high.[107]

In seven premature neonates at a postnatal age of 1 to 9 d, the corrected renal digoxin clearance correlated well with creatinine clearance, with respective mean values of 10.4 and 12.2 ml min^{-1} 1.73 m^{-2}.[108] These values were lower than those of full-term neonates. On the other hand, the $t_{0.5}$, renal clearance, and tissue distribution of digoxin were similar in newborn and adult sheep.[109] While total drug clearance and steady-state distribution volume were higher in newborns than in adults, intersubject variation was substantial.

Although animal models are used frequently to investigate digoxin kinetics, Weidler et al.[110] have shown that considerable species differences can occur. The overall distribution volume of digoxin is larger in cats than in man and dogs, whereas, the elimination rate constant β is significantly larger in dogs than in man and cats.

Evidence has been presented that renal excretion of digoxin is significantly decreased during furosemide induced diuresis.[111] The average digoxin serum $t_{0.5}$ in six healthy individuals increased from 37 h to 86 h, and urinary excretion of digoxin was transiently decreased over 10 h. The mechanism of this interaction is not known, but it may be associated with inhibition of digoxin tubular secretion or reduced renal filtration due to volume depletion. However, some other studies have reported unchanged[112,113] and increased[114] renal clearance of digoxin in the presence of furosemide.

Renal elimination of digoxin increases, and plasma levels of drug decrease, in hyperthyroidism[115] while elimination of digoxin is decreased with increasing age.[116] In seven elderly individuals (mean 81 yr), the plasma $t_{0.5}$ of digoxin was 69 h compared with 37 h in normal controls. The apparent drug distribution volume was similar in the two groups when corrected for body weight.

Both renal and nonrenal digoxin clearances were impaired by quinidine, which significantly reduced total plasma or serum clearance of digoxin in healthy subjects, by ca. 50%.[117-119] The findings were confirmed in studies of patients receiving chronic digoxin thera-