22.1 Therapeutic Implications of Digoxin Kinetics in Impaired Renal Function

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Although digoxin is largely excreted unchanged by the kidneys, many clinical and pharmacokinetic imperfections exist in calculation of digoxin dosage regimens based on renal function. Some primary concerns regarding digoxin kinetics are its variability in volume of distribution in relation to age and renal function, variability in renal clearance, the role of secondary clearance mechanisms, and the appropriateness of the pharmacokinetic methodology being employed. This report will focus on these concerns as well as the benefits of utilizing "clearance concepts" in characterizing digoxin kinetics in impaired renal function.

Variability in Digoxin Disposition

The apparent or total volume of distribution ($V_D$) serves as a proportionality constant between serum concentrations of a drug and the amount in the body and provides a means of determining the appropriate loading dose, viz:

\[
\text{Loading Dose (mg)} = V_D \times \frac{C_p^o}{F} \quad \text{(Eq. 1)}
\]

where $C_p^o$ is the initial desired postdistributive serum concentration and $F$ is bioavailability. With digoxin, the loading dose — if employed — is generally administered in three portions at 6-h intervals because of the relatively slow rate of uptake by tissues and for assessing initial patient tolerance of the drug. We have found $V_D$ values ranging from a mean of 330 liters in patients with severe renal impairment (Koup et al., 1975a) to 590 liters in young healthy adult subjects (Koup et al., 1975b). The data of Ohnhaus et al. (1974) also exhibit the extreme variability in $V_D$ (range 3.0 - 17.1 liters/kg) in patients with various degrees of renal function. This variability may partly be an artifact resulting from the mode of drug administration and the method of calculation of $V_D$. For example, greater consistency in $V_D$ values is found in cross-over studies when digoxin is given by infusion rather than by intravenous bolus injection (Koup et al., 1975b). However, the change in distribution noted in relation to renal function is also re-

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2 Unfortunately, Dr. Jusko was not able to present his paper at the symposium.
Fig. 22.1. Relationship between myocardium: serum concentration ratio of digoxin and the endogenous creatinine clearance of individual patients. Data are from Jusko and Weintraub (1974)

Reflected by differences in actual concentrations as a function of age and creatinine clearance ($Cl_{CR}$). Figure 22.1 shows the myocardium:serum concentration ratio in relation to $Cl_{CR}$ in a large group of patients (Jusko and Weintraub, 1974; Jusko, 1974). Substantiated are both the decreased tissue uptake in patients with poor renal function and the considerable variability in tissue uptake at any degree of renal function. Newborn infants exhibit an even larger $V_D$ than adults, and we have also demonstrated greater uptake of digoxin in myocardial tissue of babies in comparison with adults (Goridischer et al., 1976).

The variability in $V_D$ has led to uncertainties in deciding loading dosages of digoxin in uremic patients. The problem is whether to aim for equal serum levels or equal myocardial levels of the drug. To err on the safe side and to remain consistent with the concept of a “therapeutic serum concentration” range, we usually recommended that similar initial serum concentrations (0.7 - 1.5 ng/ml) be sought in various types of patients. However, the findings of Kramer (this symposium) may clarify the situation in suggesting that uremic patients tolerate higher serum levels of digoxin.

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