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Pharmacokinetic Variability—Disease

Pharmacokinetic data concerning specific drugs have come largely from studies in healthy, young adult subjects. This is paradoxical because drugs are used in sick people, of all ages. In the last decade, clinical scientists have directed their attention to this omission and have demonstrated the value of applying pharmacokinetics to the clinical setting. In parallel, regulatory agencies now require the pharmacokinetics of a new drug to be studied in the patient population in which it will be used.

Pharmacokinetic variability is greater in sick people than in healthy people. Disease affects various organ systems of the body and affects the way drugs are absorbed, distributed, excreted, and metabolized. Renal disease directly affects drug excretion, but also affects drug binding. Hepatic disease affects drug metabolism. Cardiovascular disease can substantially affect the transport of drugs to eliminating organs such as the liver and kidneys. These and similar considerations are the basis of this chapter.

RENAL DISEASE

Patients with renal disease need to be treated with a variety of drugs, both for their disease and intercurrent illness. Renal failure impairs the urinary excretion of drugs; drugs that are eliminated primarily by renal excretion accumulate excessively in a patient with renal insufficiency unless the dosage regimen is modified. Further complicating therapy in patients with renal disease are changes in drug distribution, potential effects on drug metabolism, and dialysis treatments.

Creatinine Clearance

Several methods are available to judge the degree of renal impairment in a patient. The most common way of assessing renal function is by determining the renal clearance of creatinine, the endogenous end product of muscle metabolism, and comparing this value to that observed in individuals of comparable size, sex, and age with normal renal function. Creatinine clearance may be measured directly or estimated indirectly from serum levels of creatinine.

Direct measurement of creatinine clearance is made by determining the amount of endogenous creatinine excreted in the urine over a 24-hr period and the creatinine concentration in the plasma during this period. Usually, blood samples are taken for creatinine determination immediately before and at the end of the urine collection period. Results of serum level determinations are averaged. The excretion rate of creatinine (expressed as mg/min) divided by the average creatinine concentration in the plasma (expressed as mg/ml) yields the endogenous creatinine clearance (in ml/min). Often, this value is normalized to a body surface area of 1.73 m^2. Normal values adjusted to 1.73 m^2 body surface area range from 140 to 180 L/24 hrs or 100 to 125 ml/min. Creatinine clearance values of 20 to 50 ml/min signify moderate renal failure; values < 10 ml/min signify severe renal failure.

Creatinine is poorly secreted and not subject to tubular reabsorption. Creatinine clearance is a useful measure of glomerular filtration rate (GFR) and although it tells us about only one aspect of renal function (i.e., filtration), it is an excellent indicator of the severity of renal disease.

This empiric observation led to the hypothesis called the intact nephron theory, which suggests that renal disease affects the entire nephron and does not selectively affect function. This hypothesis is an oversimplification of the disease process but it holds up well in clinical practice. The change in creatinine clearance should also reflect the effect

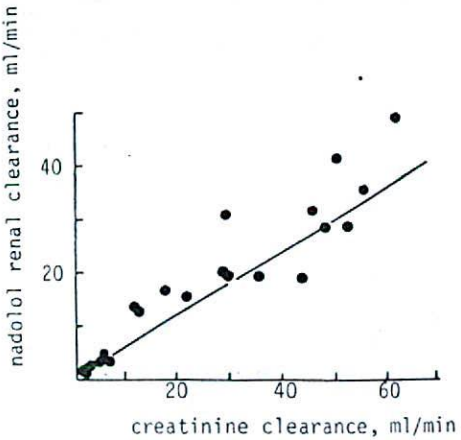

Fig. 13–1. Relationship between the renal clearance of nadolol, a β-blocker, and creatinine clearance in patients with varying degrees of renal function. (Data from Herrera, J., Vukovich, P.A., and Griffith, D.L.[2])

of renal disease on drug excretion, regardless of whether the drug is secreted or reabsorbed. This is usually the case.[1]

No other parameter of renal function other than GFR has been systematically evaluated as a quantitative index of drug excretion in patients with renal disease. It is not likely that assessment of renal blood flow or tubular function would prove more useful than GFR in developing dosage regimens for such patients.

Drug Excretion

Many studies have shown that there is a linear relationship between the renal clearance of a drug and creatinine clearance in patients with varying degrees of renal function. Figure 13–1 shows this relationship for nadolol, a relatively slowly eliminated β-blocker, in patients with hypertension.[2] The renal clearance of nadolol in essentially anephric patients is virtually zero. For nadolol and most other drugs, the following relationship applies:

$$\text{Renal clearance} = A \times \text{Creatinine clearance} \quad (13\text{–}1)$$

where A is a drug-specific constant. For nadolol, A is equal to about 0.6.

Patients with renal disease also excrete less unchanged drug in the urine than patients with normal renal function. Table 13–1 shows the cumulative amount of unchanged nadolol excreted in the urine 120 hr after an oral dose of the drug to 4 groups of patients with different degrees of renal impairment. The amount of nadolol excreted decreases with decreasing renal function.

Table 13–1. Urinary Excretion of Nadolol After a Single 80-mg Oral Dose in Patients with Varying Degrees of Renal Function*

Patient group	Creatinine clearance (ml/min per 1.73 m²)	Amount excreted (mg)
I	58	9.2
II	34	5.1
III	11	3.9
IV	2	0.6

*Data from Herrera, J., Vukovich, R.A., and Griffith, D.L.[2]

Drug Elimination

The effect of renal disease on the elimination of a drug depends on the renal status of the patient and the elimination characteristics of the drug. The clearance of a drug eliminated only by renal excretion should be markedly affected in a patient with severe renal disease, but that of a drug eliminated only by hepatic metabolism should be unaffected, unless the disease process also affects drug metabolism.

The effect of changes in renal function on the elimination of 3 types of drugs is illustrated in

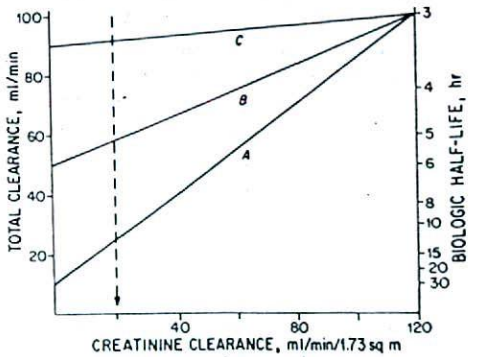

Fig. 13–2. Relationship between total clearance and renal function (creatinine clearance) for three drugs that are excreted in the urine to different degrees in patients with normal renal function. Vertical line shows clearances and half-lives when renal function is reduced to one-sixth of normal. Renal disease has the largest effect on drug A and the smallest effect on drug C. (From Gibaldi, M., and Levy, G.: Pharmacokinetics in clinical practice. I. Concepts. JAMA, 235:1864, 1976. Copyright 1976, American Medical Association.)

Figure 13–2.[3] Drugs A, B, and C are 90%, 50% and 10% eliminated by renal excretion in patients with normal renal function. After parenteral administration of drug B to patients with normal renal function, the amount of unmetabolized drug ultimately found in the urine accounts for 50% of the dose. It is assumed that the nonrenal clearance of these drugs is unaffected by kidney disease and that renal clearance is linearly related to creatinine clearance, according to Equation 13–1. Under these conditions, as shown in Figure 13–2, the total clearance of the drug from blood or plasma is also a linear function of creatinine clearance:

$$\text{Total clearance} = A \times \text{Creatinine clearance} + \text{Nonrenal clearance} \quad (13\text{–}2)$$

Figure 13–2 also shows how different the effect of renal impairment can be on the total clearance and half-life of different drugs. At a creatinine clearance of 20 ml/min per 1.73 m^2, the total clearance of drug A is decreased by 75%, that of drug B by 42%, and that of drug C by only 8.5%. The half-life of drug A increases from 3 hr in the patient with normal renal function to 30 hr in the anephric patient. The half-life of drug C hardly changes over this range of renal function.

Most cephalosporin, penicillin, and aminoglycoside antibiotics, ethambutol, flucytosine, vancomycin, lithium, and most diuretics are examples of drugs that, like drug A in Figure 13–2, are largely (> 80%) excreted unchanged.[4] Among the newer antibiotics, moxalactam[5] and cefoxitin[6] are also in this category. The total clearance of these drugs in the anephric patient will be less than 20% that measured in patients with normal renal function.

Digoxin, nadolol, and cimetidine are examples of drugs that, like drug B in Figure 13–2, are excreted unchanged in the urine to the extent of 40 to 75% of the dose.[4] Steady-state levels of these drugs are likely to be 2 to 4 times higher in anephric patients than in patients with normal renal function, unless the dosage is adjusted.

Drugs that are predominantly (i.e., > 80%) metabolized or otherwise eliminated by nonrenal mechanisms include most anticonvulsants, neuroleptics, and antidepressants, as well as digitoxin, chloramphenicol, and theophylline.

Current thinking suggests that individualized dosing of patients with renal disease be based on the relationship between total clearance and creatinine clearance expressed in Equation 13–2. Once we have cataloged the drug-specific constants (A and nonrenal clearance), we can estimate a patient's total clearance by simply plugging his creatinine clearance into Equation 13–2. This value can be compared to the total clearance of the drug in a population with normal renal function to determine if dosage adjustment is required.

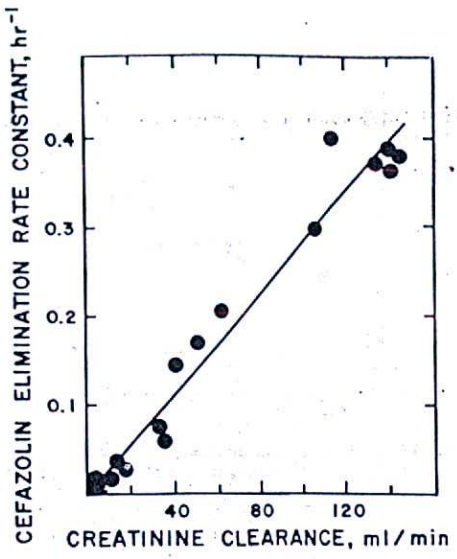

Fig. 13–3. Relationship between the elimination rate constant for cefazolin and renal function. (Data from Craig, W.A., et al.[7])

Clearance correlations are used frequently today, but the historical developments in the field have favored the use of relationships between the elimination rate constant or half-life of a drug and creatinine clearance rather than between total clearance and creatinine clearance. Therefore, to use the drug literature, one must understand this alternative approach.

Total clearance is the product of the elimination rate constant (K) of the drug and its apparent volume of distribution (V). Accordingly, the elimination rate constant of a drug will be linearly related to creatinine clearance if the volume of distribution is unaffected by renal disease. In other words,

$$K = (A/V)\,\text{Creatinine clearance} + (\text{Nonrenal clearance}/V) \quad (13\text{–}3)$$

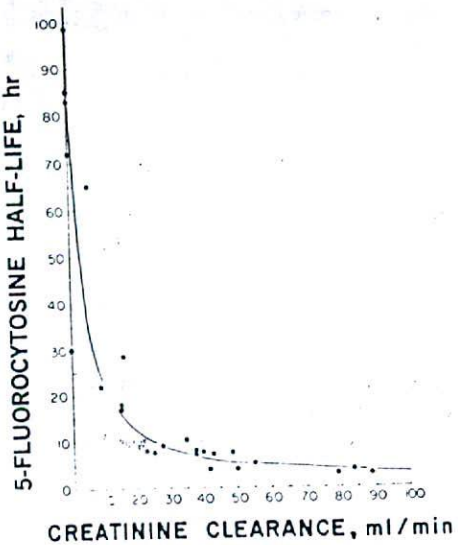

Fig. 13–4. Curvilinear relationship between the half-life of flucytosine (5-Fluorocytosine) and renal function. (Data from Schönebeck, J., et al.[10])

The relationship between renal function (creatinine clearance) and the overall elimination rate constant (K) of cefazolin, a cephalosporin antibiotic, after a single intramuscular (i.m.) dose to patients with different degrees of renal impairment is shown in Figure 13–3.[7] This kind of relationship has also been observed with nadolol,[2] cefoxitin,[6] amoxacillin,[8] and many other drugs.[1,9]

Because the half-life of a drug is reciprocally related to its elimination rate constant (i.e., $t_{1/2}$ = 0.693/K), a curvilinear relationship between half-life and creatinine clearance is expected. The correlation between the half-life of flucytosine and creatinine clearance in patients with impaired kidney function and in nephrectomized or anuric patients is shown in Figure 13–4.[10]

Estimating Half-Life

The theory previously described permits one to estimate, with relatively little information, the half-life of a drug in a patient with renal disease. Knowledge of the pharmacokinetics of the drug in patients with normal renal function and of the patient's renal status is all that is required. The usual method is best described by example.

The problem is to estimate the half-life of ampicillin in a patient who has an endogenous creatinine clearance of 10 ml/min (i.e., one twelfth of normal). Ampicillin has an average half-life of 1.3 hr (K = 0.693/$t_{1/2}$ or 0.53 hr^{-1}) in patients with normal renal function. About 70% of a parenteral dose is excreted unchanged in the urine in normal subjects (i.e., f = 0.7). The renal excretion rate constant (k_e) and nonrenal elimination rate constant (k_{nr}) in normal subjects are calculated from the product of f and K, and the product of (1 − f) and K, respectively. Thus k_e = 0.37 hr^{-1} and k_{nr} = 0.16 hr^{-1}. In the patient, the renal excretion rate constant is only one twelfth of normal or about 0.03 hr^{-1}. The nonrenal elimination rate constant is assumed to be unaffected by the disease. The overall elimination rate constant (K) is the sum of the renal and nonrenal elimination rate constants. Therefore, for this patient, K = 0.19 hr^{-1} and $t_{1/2}$ = 3.6 hr. If the patient were anephric (i.e., k_e = 0), then K = k_{nr} or 0.16 hr^{-1} and $t_{1/2}$ = 4.3 hr. In principle, this approach can be applied to any drug.[1,9]

Dosage Regimens

The half-lives of some drugs are changed sufficiently in patients with impaired renal function to warrant a change in the usual dosage regimen to prevent accumulation of the drug in the body to toxic levels. Changes in regimen usually take the form of reducing the dose per dosing interval or increasing the length of the dosing interval. Either way, there is a reduction in the total daily dose. The dosage change is usually roughly proportional to the relative difference in half-life between the patient with renal disease and the patient with normal renal function.

For example, cephalexin is administered as a 250-mg to 1-g dose every 4 to 6 hr; its average half-life in patients with normal renal function is about 0.5 to 1 hr. In a patient with a creatinine clearance of 10 to 15 ml/min, the half-life of the drug is increased about 8-fold, because cephalexin is eliminated almost solely by urinary excretion. The dosing frequency suggested for the patient with this degree of renal impairment is the usual dose every 24 hr, a dosing interval 4 to 6 times longer than usual.[11] A similar approach has been suggested for amoxacillin[8] and procainamide.[4]

Because renal clearance accounts for more than 90% of the total clearance of moxalactam in patients with normal renal function, the dose of the drug must be reduced in patients with renal disease. One group of investigators suggested that a patient

with a creatinine clearance of 50 ml/min receive half the usual dose of moxalactam at the usual time intervals and that a patient with a creatinine clearance of 10 ml/min be given 10% of the usual dose at the usual time intervals.[5]

The average half-life of digoxin is 1.6 days in patients with normal renal function but is increased to 4.4 days in anephric patients. The usual daily maintenance dose of digoxin ranges from 125 to 500 μg. The daily maintenance dose of digoxin in patients with little or no renal function, however, should be only one third to one half that used in patients with normal renal function.[12]

Renal excretion plays an important role in the elimination of all the histamine H_2-receptor antagonists currently available. About 75% of an iv dose of cimetidine is excreted unchanged in the urine. Urinary excretion accounts for about 70% of the elimination of ranitidine in patients with normal renal function. Sixty-five to 70% of an iv dose of famotidine and about two-thirds of an oral dose of nizatidine is excreted unchanged.

The pharmacokinetics of intravenous famotidine in patients with impaired renal function has been studied by Halstenson et al.[13] Patients were grouped on the basis of creatinine clearance (CrCl) as follows: mild renal impairment (CrCl = 30 to 60 ml/min); moderate-to-severe (CrCl = 10 to 30 ml/min); end-stage (CrCl < 10 ml/min). The average terminal half-life was about 9 hr for patients with mild or moderate-to-severe impairment but increased to about 18 hr in patients with end-stage renal impairment.

The clearance of famotidine decreased in a predictable fashion with decreasing renal function. Mean clearance was 109 ml/min in patients with mild impairment, 69 ml/min in those with moderate-to-severe failure, and 42 ml/min in anuric patients. Renal clearance accounted for nearly 60% of famotidine elimination in the mild group and about 30% in the moderate-to-severe group. Nonrenal clearance held constant at about 40 ml/min in all three groups.

The investigators concluded that because the apparent volume of distribution of famotidine does not vary with renal function, the dose in patients with renal impairment may be similar to that used for patients with normal renal function. However, because of decreased clearance in such patients, the dosing interval may need to be increased to avoid excessive drug accumulation and potential toxicity.

The angiotensin-converting enzyme (ACE) inhibition activity of enalapril resides largely in a diacid metabolite, enalaprilat, which is formed by hydrolysis of enalapril in the liver. Enalaprilat is extensively excreted unchanged. Lowenthal et al.[14] found that the total area under the enalaprilat concentration in serum versus time curve after a single oral dose of enalapril was 4 to 6 times greater in patients with creatinine clearance values ranging from 10 to 79 ml/min than in patients with normal renal function.

The prolonged reduction in blood pressure seen in patients with chronic renal failure is probably related to the elevated plasma levels of enalaprilat. Lowenthal et al. recommend that lower doses or less frequent dosing of enalapril be considered when treating hypertension in patients with renal insufficiency.

Patients with renal failure sometimes need loading doses because the time required to reach steady state with a particular drug may be much longer than in patients with normal renal function. This principle is particularly important when planning antibiotic or cardiac glycoside therapy.

The two methods for reducing maintenance dosage in patients with renal disease, lengthening the dosing interval or reducing the unit dose, are attractive because the required changes are easily calculated. However, when dosing interval extension is applied in severe renal disease to drugs with short half-lives, like the aminoglycoside antibiotics, prolonged periods of serum concentrations below the therapeutic range may result (Fig. 13–5).[15] On the other hand, administration of smaller doses with the usual frequency results in lower peak concentrations, which may be subtherapeutic, and higher trough concentrations, which may enhance the nephrotoxicity of the aminoglycoside antibiotics.[15]

With certain drugs it is best to combine dosage reduction with a change in the dosing interval. For example, the usual dose of carbenicillin required to maintain an average plasma concentration of 50 μg/ml in patients with normal renal function is about 1 g every 4 hr. The recommended dose to maintain equivalent levels in a patient with a creatinine clearance of 10 ml/min is 0.4 g every 8 hr.[16] This recommendation lowers the unit dose by 60% and doubles the dosage interval; it yields a drug concentration profile more similar to that observed in patients with normal renal function than would either dosage adjustment strategy alone.

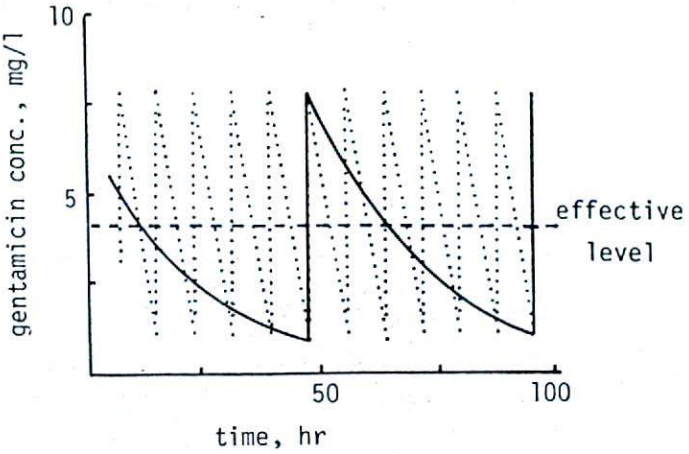

Fig. 13–5. Steady-state serum concentration profile for gentamicin in a patient with normal renal function who is given 1.7 mg/kg every 8 hr (stippled line) and in a patient with a creatinine clearance of 20 ml/min (one sixth of normal) who is given 1.7 mg/kg every 48 hr (solid line). (Data from Chennavasin, P., and Brater, D.C.[15])

Similar recommendations for aminoglycoside antibiotic dosage in renal failure have been reviewed by Chennavasin and Brater.[15]

It may also be prudent to change both the dose and dosing interval of vancomycin in patients with renal impairment. The use of this agent has increased dramatically in recent years because of the prevalence of infections caused by methicillin-resistant *Staph aureus* and the increased employment of prosthetic implants, which may become infected with *Staph epidermidis*. In patients with normal renal function, vancomycin is largely excreted unchanged.

Rodvold et al.[17] studied the kinetics of iv vancomycin in adult patients with various degrees of renal function, who were receiving the drug for treatment of gram-positive infections. Patients were categorized into three groups based on measured creatinine clearance: > 70, 40 to 70, and 10 to 39 ml/min per 1.73 m^2.

Vancomycin clearance decreased in a predictable manner, averaging 98 ml/min/1.73 m^2 in group 1, 53 in group 2, and 31 in group 3. Renal clearance accounted for about 90% of the total clearance of vancomycin in patients with normal renal function but for only 63% in patients with CrCl values less than 40 ml/min/1.73 m^2.

On the basis of these results, Rodvold et al. developed dosage guidelines. Their goal was to maintain peak levels of vancomycin in patients with impaired renal function similar to those seen in patients with normal renal function. They accomplished this by decreasing the daily dose while extending the dosing interval. They proposed the following algorithm for daily dose:

$$\text{Daily Dose (mg/kg)} = 0.227\ \text{CrCl} + 5.67 \quad (13\text{–}4)$$

where CrCl is expressed as ml/min per 70 kg. Practical dosing intervals ranged from every 8 hr to every 48 hr, based on renal function. The investigators suggested that vancomycin is to be given 3 times a day in patients with CrCl > 65 ml/min per 70 kg, once a day in patients with CrCl values of 20 to 39, and every other day in patients with CrCl values of 10 to 19.

A comprehensive guide to drug usage in adult patients with impaired renal function is available.[4] This guide consists of tables listing recommended dosing intervals of a wide variety of drugs for patients with mild, moderate, and severe renal failure. In most instances, the recommended dosing intervals are based on the clinical and pharmacokinetic principles discussed in the preceding paragraphs. More descriptive information on specific drugs is also available in two review articles concerned with drug prescribing in renal failure.[18,19] A nomogram for dosage adjustment in patients with renal failure is also available.[20]

Hemodialysis

Patients with renal failure may require intermittent hemodialysis, which can substantially augment the clearance of certain drugs in anephrics. Factors that influence drug removal during conventional hemodialysis are the molecular weight, lipid solubility, and binding of the drug, and the efficiency of the dialyzer.[21] Water-soluble drugs that have a molecular mass of less than 500 daltons and a small volume of distribution and that are poorly plasma protein bound are easily removed during dialysis.

One study in anephric patients found that the half-life of cephalexin was 6.3 hr on hemodialysis and 31 hr without dialysis.[11] The mean serum half-life of carbenicillin in anuric patients during hemodialysis was 4.3 hr compared to 14.6 hr off hemodialysis.[16] Large effects of hemodialysis have also been observed with nadolol,[2] cefoxitin,[6] amoxacillin,[8] cefamandole,[22] and other drugs.[21]

Dosage regimens for patients with renal failure that are developed without accounting for increased drug clearance during hemodialysis may result in periods of subtherapeutic drug levels. One report that recommends appropriately reduced dosing schedules for carbenicillin in anephric patients and in patients with severe renal impairment also advises that an additional 0.75 g or 1.5 g, depending on the desired steady-state level, should be given at the termination of each 6-hr hemodialysis to replace expected losses.[16]

Specific and sometimes complicated recommendations have been made to overcome the problem of drug removal during hemodialysis, but most clinical situations do not demand such rigorous approaches. It is common practice simply to replace one full maintenance dose for each dialysis period for drugs that are significantly cleared by conventional hemodialysis.[18]

Serum Creatinine

The difficulty in obtaining accurate 24-hr urine collections in patients for the purpose of estimating endogenous creatinine clearance has stimulated interest in other indicators of renal function that are easier to measure and might prove useful in predicting changes in drug elimination. One possibility is blood urea nitrogen (BUN). Although BUN is elevated in kidney disease, its level correlates poorly with creatinine clearance. On the other hand, serum creatinine, which is also elevated in patients with impaired renal function, appears to correlate well with creatinine clearance.

Two reports have compared 24-hr creatinine excretion and serum creatinine concentrations as indicators of renal function.[23,24] Both conclude that serum creatinine levels are superior to measured creatinine clearances for the detection of abnormal glomerular function and of changes in glomerular function in patients with chronic renal disease. Morgan and co-workers propose that direct measurement of creatinine clearance be abandoned as a routine measure of glomerular function.[23]

The use of serum creatinine concentrations to determine renal function has been reviewed in considerable detail by Lott and Hayton[25] and by Bjornsson.[26] Normal serum creatinine concentrations vary from 0.6 to 1.0 mg per 100 ml (mg/dl) in women and 0.8 to 1.3 mg/dl in men. In principle, the following equation describes the relationship between creatinine clearance (CrCl) and serum creatinine concentration (SCC) in a patient with stable renal function:

$$CrCl = k_o/SCC \qquad (13\text{–}5)$$

where k_o is the endogenous creatinine production rate. Serum creatinine remains constant unless there is a change in the rate of production of creatinine or in creatinine clearance

It would be a simple matter to estimate creatinine clearance from SCC values if k_o were the same for everyone. Of course, this is not the case. The production rate of endogenous creatinine varies as a function of age, body weight, and sex.

Because creatinine production is proportional to lean body mass and inversely proportional to age, investigators have been able to develop formulas and nomograms for estimating creatinine clearance without the need for urine collection. The following equation is particularly useful;[27] it has been validated in hundreds of nonobese adult patients of both sexes with widely varying degrees of renal function:

$$CrCl = \frac{(140 - age)\,(body\ weight)}{72 \times SCC} \qquad (13\text{–}6)$$

Age is expressed in years, body weight in kg, and SCC in mg/dl. The same equation is used for male and female patients, but the value determined should be reduced by 15% for a female patient.[27]

According to Equation 13–6, a 20-yr-old, 70-kg male patient with a serum creatinine of 1 mg/dl has a creatinine clearance of 117 ml/min. The same patient with an elevated serum creatinine of 5 mg/dl has a creatinine clearance of 23 ml/min.

Table 13–2. Some Clinically Important Active or Toxic Drug Metabolites that Accumulate in Renal Failure

Drug	Metabolite
Allopurinol	Oxipurinol
Clofibrate	Chlorophenoxyisobutyric acid
Meperidine	Normeperidine
Procainamide	N-Acetylprocainamide
Propoxyphene	Norpropoxyphene

An 80-yr-old, 70-kg man with an apparently normal serum creatinine of 1 mg/dl has a creatinine clearance of only 58 ml/min.

Equation 13–6 applies to a remarkably large segment of the population. It overestimates measured creatinine clearance in the pregnant patient and may overestimate creatinine clearance in patients with edema or ascites.[18] Creatinine clearance is also overestimated in at least some patients with liver disease[28] and in obese patients, when total body weight is used in Equation 13–6.[29] Estimation of creatinine clearance from serum creatinine in obese patients is particularly difficult because substituting ideal body weight for total body weight in Equation 13–6 may also yield incorrect estimates of creatinine clearance.[29]

The estimation of creatinine clearance from serum creatinine in pediatric patients has also been evaluated, and clinically useful relationships have been developed.[30,31]

Effects on Metabolized Drugs

The rather simple theory used to explain and predict the influence of renal disease on drug elimination assumes that the pharmacokinetics of drugs eliminated by hepatic metabolism is unaffected by impairment of renal function. This is not always the case.

The incidence of adverse effects of certain highly metabolized drugs like phenytoin, clofibrate, and diazepam is higher in patients with renal disease than in patients with normal renal function. This may be related to changes in plasma protein binding that are evident in chronic renal failure and are discussed later in this chapter. Alternatively, drug metabolism may be inhibited or there may be the accumulation of metabolites that have pharmacologic activity but that are ordinarily excreted in the urine.

Patients with impaired renal function may experience severe and prolonged respiratory depression when treated with morphine, although morphine is extensively metabolized.[32] Improbably, this has been attributed to accumulation of the drug during renal failure. Wolff et al.[33] studied the influence of renal function, as determined by the clearance of labeled EDTA, on morphine and morphine glucuronide pharmacokinetics in patients with various chronic renal diseases after a single iv dose of morphine. No relationship was found between total body clearance of morphine and renal function, but patients with renal insufficiency had impaired elimination of morphine glucuronides. The apparent clearance of the glucuronides was significantly correlated with EDTA clearance ($r = 0.94$).

These results suggest that the accumulation of a morphine metabolite, most likely morphine 6-glucuronide, rather than of morphine itself is the cause of enhanced activity and toxicity of morphine in patients with renal failure. Morphine 6-glucuronide crosses the blood-brain barrier, has a high affinity for the opioid receptor, and has opioid agonist activity.

The pharmacokinetic and clinical implications of drug metabolites in renal failure have been reviewed by Verbeeck and Branch.[34] Table 13–2 lists some clinically important active or toxic drug metabolites that accumulate in renal failure.

Several recent reports have addressed the regeneration of parent drug from glucuronide conjugates that accumulate in patients with renal failure. The net effect of this conversion is a decreased clearance of the parent drug. In the case of lorazepam,[34] diflusinal,[35] and clofibrate,[36] it appears that when the renal excretion of the glucuronide conjugate is impaired, the conjugate accumulates in plasma where it is hydrolyzed to regenerate parent drug.

Renal failure may also produce a more direct inhibition of drug metabolism. This has been elegantly demonstrated by Terao and Shen.[37] They found that first-pass metabolism of the l-isomer of propranolol was reduced in rats with chemically-induced acute renal failure. When livers from normal rats were perfused with diluted blood from normal rats, a very high extraction ratio was observed. Less than 3% of the dose escaped first-pass metabolism. The extraction of l-propranolol was significantly lower when livers from rats with acute renal failure were perfused with diluted blood from uremic rats. The percent of dose evading first-metabolism increased more than 3-fold, from 2.6% to 9.4%.

An interesting question arises from these observations. Does the basis for the impaired first-pass

metabolism reside in the uremic liver or in the uremic blood? Terao and Shen found that when livers from normal rats were cross-perfused with uremic blood, first-pass metabolism was decreased to almost the same level as when livers from renal failure rats were perfused with uremic blood. The percent of dose evading first-pass metabolism was 7.3%. In contrast, livers from renal failure rats cross-perfused with normal blood exhibited l-propranolol extraction comparable to normal livers perfused with normal blood. The percent of dose evading first-pass metabolism was 3%.

The investigators concluded that the decrease in presystemic hepatic extraction of l-propranolol in the rat model of acute renal failure is due to the presence of an inhibitory factor in uremic blood. No apparent changes in the intrinsic activities of the hepatic transport and/or drug metabolizing enzyme systems were observed. They caution, however, that although the microsomal cytochrome P450 enzymes responsible for the biotransformation of propranolol did not appear to be affected by acute renal failure, this may not be the case in chronic renal failure.

Reduced drug metabolism had also been observed in patients with renal failure given encainide,[38] an antiarrhythmic agent eliminated almost entirely by oxidative metabolism. After a single iv and oral dose of encainide, its systemic and oral clearances were significantly lower in patients with renal failure than in healthy human subjects. Chronic oral dosing to steady state resulted in nearly a 2-fold increase in levels of O-desmethylencainide (ODE), the most important active metabolite, and a 3-fold increase in levels of 3-methoxy-ODE, another active metabolite, compared with levels measured in healthy subjects. The investigators concluded that patients with renal failure will require lower doses of encainide because of reduced clearance of encainide and increased accumulation of active metabolites.

End-stage renal disease also affects the disposition of sulindac. Sulindac is a prodrug. Ordinarily, it undergoes two major biotransformations: irreversible oxidation to an inactive sulfone metabolite and reversible reduction to a pharmacologically active sulfide metabolite.

Gibson et al.[39] determined areas under the plasma level-time curves (AUCs) after a single oral dose of sulindac to patients with end-stage renal failure. The AUC values for sulindac and the sulfone were similar to values measured in control subjects, but the AUC for the sulfide was only about one-third that found in controls.

Plasma protein binding of sulindac as well as binding of its two major metabolites was found to be lower in patients with renal failure. When corrected for protein binding, the AUC values for sulindac and the sulfone were twice that of controls, whereas that of the sulfide was about half the AUC determined in control subjects. The investigators concluded that end-stage renal failure impairs the reduction of sulindac to the active sulfide, whereas oxidation to the sulfone appears to be intact. These patients may require higher than normal doses of sulindac to achieve adequate control of rheumatic symptoms.

LIVER DISEASE

When hepatic metabolism is an important route of drug elimination, dysfunction of the liver could lead to changes in the pharmacokinetics of the drug. The clinical significance of the changes in drug metabolism, however, depends on the type and severity of the disease and on the pharmacokinetics of the drug. In a survey of some 30 investigations with many different drugs, only about two thirds of the studies showed a significant difference in drug elimination between patients with liver disease and patients or subjects with normal liver function.[40] No differences were reported for chlorpromazine, dicumarol, phenytoin, or salicylate. Other reports suggest that mild to moderate acute viral hepatitis has no effect on the disposition of warfarin[41] and that liver cirrhosis has little effect on the elimination of acetaminophen.[42]

The effects of liver disease on the pharmacokinetics of drugs are unpredictable, but clearly the elimination of some potent drugs is impaired in patients with chronic liver disease. The lack of predictability relates to the multiple effects that liver disease produces, effects on drug metabolizing enzymes, on drug binding, and on hepatic blood flow. It also relates to the complexity of hepatic metabolism; some enzyme systems seem to be far more sensitive to the effects of disease than other systems. Because of the lack of predictability, review articles that enumerate the effects of different hepatic diseases on the pharmacokinetics of specific drugs are useful to the physician and pharmacist in formulating dosage requirements for the individual patient.[43] A more recent guide to drug dosage in hepatic disease is also available.[44]

Considerable progress has been made during the last decade in our understanding of the effects of liver disease on drug disposition. A great deal of the literature has been reviewed by Howden et al.[45]

Antipyrine

Antipyrine has been used widely as a model drug to investigate the effects of liver disease on drug metabolism in man. Because antipyrine is negligibly bound to plasma proteins and tissues, and because it is eliminated almost exclusively by hepatic metabolism with a low hepatic extraction ratio, its half-life and clearance are considered sensitive indicators of liver function with respect to oxidative metabolism.

The usual procedure for calculating antipyrine clearance involves collection of 4 to 7 samples of blood or saliva during a 24 to 48 hr period after oral or iv administration of a single dose. To determine whether this procedure could be simplified, the usual method was compared in a large number of subjects with one based on the determination of antipyrine concentration in a single blood sample and an estimated volume of distribution.[46]

When the single sample was taken 18 to 27 hr after antipyrine administration, correlation coefficients between the one-point method and the customary method ranged from 0.97 to 0.99 and regression coefficients approximated unity. Useful correlations were obtained simply by assuming a volume of distribution of 40 L (total body water) for all subjects; more sophisticated estimates of total body water based on lean body weight, age, sex and height improved the correlation.

The term liver disease encompasses several distinct hepatic diseases, not a single disease entity. The particular disease and its severity are factors in drug metabolism. This is clearly seen in a study evaluating antipyrine half-life in patients with various liver diseases.[47] In general, the half-life of antipyrine was prolonged in these patients compared to that found in healthy subjects. Patients with chronic liver disease, however, showed a greater increase in half-life than those with acute, reversible conditions.

Compared to healthy subjects who had an average half-life of 12 hr, patients with cirrhosis and chronic active hepatitis had average antipyrine half-lives of 34 hr and 26 hr, respectively. Certain individuals in both groups had half-lives on the order of 50 hr. On the other hand, patients with acute hepatitis or obstructive jaundice showed relatively

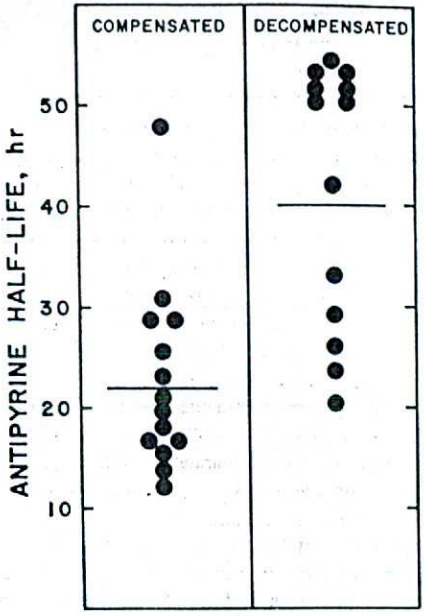

Fig. 13–6. Comparison of antipyrine half-life in patients with compensated liver disease (serum albumin >3 g dl, prothrombin index >80%) and in patients with decompensated liver disease (serum albumin <3 g/dl, prothrombin index <80%). (Data from Branch, R.A., Herbert, C.M., and Read, A.E.[47])

small differences in antipyrine half-life from that found in normal subjects.

The most marked prolongation in antipyrine half-life was found in association with hypoalbuminemia and hypoprothrombinemia, suggesting that these changes were the result of or related to altered synthesis of microsomal enzyme protein.[47] Antipyrine half-lives in patients with "compensated" liver disease and in patients in whom the disease was "decompensated" are shown in Figure 13–6. Compensated patients had a serum albumin higher than 3 g/dl and a prothrombin index above 80%. Serum albumin and prothrombin index in the decompensated group were less than 3 g/dl and below 80%.

Mehta et al.[48] studied antipyrine kinetics before and after liver transplantation in 5 patients. After transplantation, there was a significant increase in antipyrine clearance and a marked decrease in antipyrine half-life. Mean clearance was 16.6 ml/min before and 36 ml/min after transplantation. Mean half-life decreased from 28 to 13 hr.

In another study, the total clearance of antipyrine

was determined in healthy subjects, in patients with cirrhosis, and in patients with severe liver disease before, during, and after hepatic encephalopathy.[49] The average antipyrine clearance in control subjects was about 51 ml/min. Patients with cirrhosis but no sign of encephalopathy showed an average antipyrine clearance of 17 ml/min. Antipyrine clearance measured in patients during hepatic encephalopathy (4.6 ml/min) was significantly lower than that of patients investigated 4 wk before or after encephalopathy (9.6 ml/min).

Table 13–3 shows the results of liver function tests and antipyrine clearance over a 5-month period in a patient with reversible hepatic encephalopathy. During the acute phase of the disease, results of all liver function tests were grossly abnormal; antipyrine clearance was depressed to 5.9 ml/min. Table 13–3 also shows that certain biochemical tests are poor indicators of the liver's ability to metabolize antipyrine. For example, 1 month after the first examination, galactose elimination and prothrombin index had returned to the normal range but antipyrine clearance was still only about one half of normal. Andreasen and Ranek suggest that the antipyrine clearance may serve as a quantitative measure of liver function and that it may be useful as a prognostic indicator of acute liver failure.[49]

Other Drugs with a Low Hepatic Extraction Ratio

The elimination of drugs that have a low hepatic extraction ratio and are largely cleared by metabolism in the liver is rate limited by the activity of hepatic drug metabolizing enzymes. The clearance of these drugs should be sensitive to changes in hepatic enzymes secondary to disease. A given liver disease, however, does not affect all enzyme pathways to the same extent. Therefore, the elimination of certain low extraction ratio drugs, such as warfarin, salicylate, and phenytoin, is seemingly unimpaired by liver disease, at least in some cases.

Most drugs with low hepatic extraction ratios are like antipyrine in that their elimination is impaired in patients with moderate to severe hepatic disease. Many studies have been directed to the elimination of benzodiazepines in patients with hepatic dysfunction, particularly to the elimination of diazepam.[50]

The clearance of diazepam in patients with alcoholic cirrhosis is only about half that in age-matched control subjects. The half-life of the drug is increased about 4-fold over control values because of a decrease in clearance and an increase in apparent volume of distribution, consistent with reduced plasma protein binding of diazepam in the cirrhotics (Table 13–4).[51] These findings have been confirmed by other investigators.[52–54]

Branch and co-workers reported a significant correlation between the clearance of diazepam, or the dose of a constant rate intravenous infusion of diazepam required to produce a given degree of sedation, and the severity of the disease, as judged by serum albumin concentration.[53] Correlations between diazepam clearance and biochemical indices of the disease process were also found by Greenblatt and associates.[54]

In another study, Ochs et al.[55] gave a 5-mg dose of diazepam once daily for 3 weeks to patients with biopsy-proven cirrhosis and to healthy control subjects of similar age and weight. Steady-state levels of diazepam were 98 ng/ml in control subjects and 165 ng/ml in patients with liver disease. Corresponding levels of the active metabolite of diazepam, desmethyldiazepam, were about twice as high in patients with hepatic cirrhosis as in healthy subjects.

Sedation increased with time in all subjects during diazepam administration. Sedative effects, however, were significantly greater in cirrhotic

Table 13–3. Liver Function Tests and Antipyrine Clearance in a Patient with Reversible Hepatic Encephalopathy*

Date of examination	Hepatic encephalopathy	Galactose elimination (mmol/min)	Prothrombin (%)	Bilirubin (μmol/L)	Alanine amino-transferase (U/L)	Antipyrine clearance (ml/min)
July 7, 1973	Yes	1.1	12	540	430	5.9
July 25, 1973	No	1.6	57	454	130	13.5
August 9, 1973	No	1.7	129	107	70	29.3
December 4, 1973	No	2.2	94	15	10	54.5
Normal values		1.4–3.5	85–115	<17	5–25	50 ± 14

*Data from Andreasen, P.B., and Ranek, L.[49]

Table 13–4. Pharmacokinetic Parameters of Diazepam in Patients with Alcoholic Cirrhosis and in Age-Matched Control Subjects*

Parameter	Control	Alcoholic cirrhosis
Age, yr	44	46
Half-life, hr	27	106
Clearance, ml/min	27	14
Volume of distribution, l/kg	1.1	1.7
% Unbound in plasma	2.2	4.7

*Data from Klotz, U., et al.[51]

than in control subjects. Reduction of the daily diazepam dose by about 50% is probably appropriate for patients with hepatic cirrhosis.

Substantially impaired metabolism and changes in volume of distribution have also been found with chlordiazepoxide in patients with cirrhosis or acute viral hepatitis,[56] but not with oxazepam or lorazepam.[50] The elimination of diazepam and chlordiazepoxide primarily involves oxidative metabolism, whereas oxazepam and lorazepam are metabolized by glucuronic acid conjugation. In view of these differences, oxazepam and lorazepam are preferred for patients with liver disease.

The clearance of theophylline is also reduced in patients with liver disease,[57,58] particularly those with decompensated liver cirrhosis.[59] One study reported that patients with cirrhosis had a much longer half-life of theophylline (26 hr vs 7 hr) when compared to healthy subjects.[57] Another study found a significant correlation between theophylline clearance and serum bilirubin levels in patients with cirrhosis.[58] The maintenance dose of theophylline usually must be reduced in patients with liver disease to avoid toxicity.

In principle, one would expect liver disease to have little effect on the elimination of cimetidine because more than 60% of an iv dose is excreted unchanged in the urine. Nevertheless, the common use of cimetidine to treat peptic ulcers associated with chronic liver disease prompted a study to examine the effects of cirrhosis on the disposition of cimetidine.[60]

Cimetidine clearance after iv administration was similar in patients with chronic liver cirrhosis and in control subjects with ulcers, but nonrenal clearance was significantly smaller in patients with cirrhosis. Apparent volume of distribution of cimetidine was larger in cirrhotics but oral bioavailability was about the same in each group, about 70–75%. Irrespective of route of administration, patients in the control group excreted a smaller fraction of the dose as unmetabolized cimetidine.

Plasma levels of cimetidine after oral administration tended to be higher in patients with cirrhosis than in control patients. The time after a single oral dose during which plasma levels exceeded 0.5 mg/L was 205 min in controls and 295 min in cirrhotics. Clinically, liver disease would seem to require reduction of cimetidine dose only in the elderly or severely sick patient. The association between cimetidine and mental confusion occurs primarily in patients with organ failure and of advanced age.

The important role of hepatic metabolism in the activation and elimination of sulindac and its sulfide metabolite prompted Juhl et al.[61] to study the pharmacokinetics of sulindac in patients with confirmed alcoholic liver disease. Patients were divided into two groups based on their ability to eliminate indocyanine green (ICG), a marker of hepatic blood flow and hepatic function. Patients with ICG half-lives greater than 10 min were considered to have poor hepatic function; those with half-life values less than 10 min were classified as having fair hepatic function.

Serum levels of sulindac and its sulfide after a single oral dose of sulindac were considerably higher in patients with poor liver function than in healthy subjects. AUC values were 37 vs 13 μg-hr/ml for sulindac and 39 vs 10 μg-hr/ml for the sulfide. Average blood levels of the sulfide, the active form of the drug, were nearly 4 times higher in patients with poor hepatic function than in healthy subjects. The clinical consequences of these findings are uncertain, but the results suggest that sulindac be used cautiously in patients with poor hepatic function.

Fluoxetine is a novel antidepressant, chemically unrelated to the large group of tricyclic compounds widely used for the treatment of depression. The drug is well absorbed after oral administration, 94% bound to plasma proteins, and demethylated, presumably in the liver, to an active metabolite, norfluoxetine. The half-life of the parent drug is about 4 days and the half-life of the active metabolite is about 7 days.

Schenker et al.[62] studied the disposition of oral fluoxetine in healthy male subjects with normal liver function and in male patients with stable alcoholic cirrhosis. The total AUC following a single dose of fluoxetine was nearly twice as large in

patients for both fluoxetine and its metabolite. The oral clearance of fluoxetine was 9.6 ml/min/kg in control subjects and 4.2 ml/min/kg in patients with cirrhosis.

The investigators suggested that at steady state both fluoxetine and norfluoxetine levels will be higher in patients with cirrhosis, unless the dosage is reduced. A 50% reduction would appear appropriate for the well-compensated cirrhotics examined in this study but a larger reduction may be needed in sicker patients. Unfortunately, conventional liver tests and ICG clearance did not correlate well with the apparent clearance of fluoxetine in individual patients, so extrapolation is not possible.

The pharmacokinetics of flecainide have also been studied in patients with documented cirrhosis of the liver.[62] All patients had abnormal values for most of the routine liver functions tests, and for albumin levels and prothrombin time. The mean, weight-adjusted, apparent clearance after a single oral dose of flecainide was reduced 60% in patients with cirrhosis compared with healthy control subjects. Renal clearance of flecainide was similar in each group. The average ratio of renal clearance to total clearance was 0.40 for healthy subjects and 0.83 for patients with cirrhosis of the liver, indicating that in patients with cirrhosis much less flecainide is eliminated by biotransformation than by renal excretion of unchanged drug.

Plasma levels of flecainide in patients with liver disease may accumulate to unacceptably high levels with usual therapeutic dosage regimens. According to McQuinn et al.,[63] in such cases, "the use of plasma level monitoring as a guide for dosage adjustments is very important." Particular caution must be exercised when flecainide is given to patients with liver disease along with other drugs known to inhibit drug metabolism.

Enalapril, like sulindac, requires bioactivation. The conversion of enalapril to enalaprilat appears to occur in the liver and it is important to know the pharmacokinetics and pharmacodynamics of enalapril in patients with cirrhosis. Ohnishi et al.[64] determined these parameters in biopsy-proven cirrhotic patients and healthy control subjects after oral administration of enalapril.

The peak concentration of enalapril after a single oral dose was nearly twice as high in the cirrhotic patients as in the controls and mean apparent clearance was much lower in the patients with liver disease (653 vs 1527 ml/min). Serum levels of enalaprilat, the active form of enalapril, in patients with cirrhosis, were less than half those observed in control subjects.

The clinical implications of this study are unclear. Although the results suggest that the bioactivation of enalapril to enalaprilat is substantially impaired in patients with cirrhosis, the effects of the drug on blood pressure, heart rate, serum angiotensin-converting enzyme, and plasma renin activity appeared to be unaffected. The investigators cautioned that "the full therapeutic implication of the findings from this single-dose study must await further multiple-dose studies in patients with cirrhosis."

High Hepatic Extraction Ratio Drugs

Cirrhosis and other liver dysfunctions affect not only hepatic drug metabolizing enzymes but also liver blood flow.[65] Thus, hepatic disease can affect the disposition of high hepatic extraction ratio drugs in two ways. After oral administration, presystemic metabolism will be less in a cirrhotic patient than in a patient with normal hepatic function; the same oral dose may produce higher blood levels in the cirrhotic patient because systemic availability is greater. Once the drug is in the bloodstream, its clearance is lower in the cirrhotic patient than in the healthy individual because of reduced hepatic perfusion and decreased hepatic enzyme activity.

Indocyanine green (ICG) is eliminated so rapidly by the human liver that its clearance is often used as an indicator of hepatic blood flow rate. The disposition of intravenous ICG and lidocaine, another high hepatic extraction ratio drug, was studied in patients during and after recovery from an episode of acute viral hepatitis.[66] On the average, the clearance of both drugs was about 40% lower during the acute phase than after recovery. A similar decrease in ICG clearance has been found in patients with chronic liver disease.[67] These observations are consistent with the idea that a reduction in liver blood flow will decrease the clearance of drugs with high intrinsic hepatic clearance.

The importance of liver blood flow in the disposition of drugs with a high hepatic extraction ratio has been elegantly demonstrated by Feely et al.[68] with lidocaine in patients with orthostatic hypotension. They found that an abrupt change in position from supine to upright in healthy subjects resulted in an average decrease in mean arterial pressure (MAP) of only 2 mm Hg and a mean fall of about 5% in liver blood flow, estimated using ICG clearance. In patients with idiopathic ortho-

static hypotension, however, a change in position resulted in a 24 mm Hg drop in MAP and a 30% decrease in liver blood flow.

The patients with orthostatic hypotension were studied on a second occasion to determine lidocaine clearance as a function of MAP and hepatic blood flow. Each subject received a 60 mg iv injection of lidocaine over 2 min, first in the supine position and then in the tilted (upright) position. MAP fell from 91 to 67 mm Hg when the table was tilted. Peak concentration of lidocaine was nearly twice as high in the upright than in the supine position. Lidocaine clearance decreased from 602 ml/min in the supine position to 475 ml/min in the upright position.

The clearance of propranolol is also lower in patients with alcoholic cirrhosis than in healthy subjects (580 ml/min vs 860 ml/min). After oral administration, systemic availability is 38% of the dose in control subjects and 54% in cirrhotic patients. The steady-state free drug concentration of propranolol following repetitive oral dosing is about 3 times higher in patients with cirrhosis than in control subjects, reflecting increased bioavailability, decreased clearance, and an increase in fraction free in the plasma.[69]

Similar results have been observed with metoprolol, another high hepatic extraction ratio β-blocker.[70] Bioavailability was 84% in patients with hepatic cirrhosis and 50% in a control group. The total body clearance of metoprolol was 0.61 L/min in cirrhotic patients and 0.80 L/min in the control subjects.

Dramatic increases in the systemic availability of oral analgesics have been observed in patients with cirrhosis. Intravenous and oral studies with pentazocine and meperidine in patients with moderate cirrhosis and in age-matched healthy subjects found that, compared to control subjects, there was a 46% decrease in the clearance of pentazocine and a 278% increase in bioavailability, and a 36% decrease in the clearance of meperidine and an 81% increase in bioavailability in cirrhotic patients.[71]

Consistent with theory, these studies suggest that the higher the intrinsic hepatic clearance of a drug, the larger is the increase in systemic availability of the drug in patients with cirrhosis. The decrease in clearance and increase in bioavailability have large effects on blood levels of the drug after oral administration. One eighth the dosage of pentazocine and one third the dosage of meperidine is required in cirrhotic patients to produce blood levels comparable to those in healthy subjects after usual doses.[71]

Triamterene is a potassium-sparing diuretic that is efficiently metabolized by the liver and subject to a considerable first-pass effect on oral administration. Villeneuve et al.[72] studied the pharmacokinetics of triamterene in healthy control subjects and in patients with severe alcoholic cirrhosis. Each subject received a single 200 mg oral dose.

A profound difference was observed between the two groups. Mean oral clearance was 1617 ml/min in the control subjects but only 134 ml/min in patients with liver disease. The ratio of p-hydroxytriamterene sulfate, a primary metabolite, to triamterene in plasma was 7.18 in the healthy subjects and 0.55 in the patients with cirrhosis.

The change in triamterene kinetics in patients with severe alcoholic cirrhosis resulted in prolongation of its natriuretic effect from 8 hr in control subjects to 48 hr in the patients. The overall diuretic response, however, as estimated by the cumulative increase in sodium excretion over 48 hr, was similar in both groups.

Nifedipine and related calcium channel blockers are less than completely available after oral administration because of first-pass metabolism. Kleinbloesem et al.[73] studied nifedipine in 7 patients with liver cirrhosis and in an equal number of age-matched healthy control subjects. All of the patients had varices and 3 had a portacaval shunt.

After an iv dose, nifedipine levels persisted far longer in patients with cirrhosis than in matched controls. The half-life of nifedipine was 420 min in patients and 111 min in controls. Clearance was decreased by more than 50%; mean values of 588 ml/min were calculated in controls and 233 ml/min in patients with cirrhosis. The unbound fraction of nifedipine in plasma was almost doubled in patients with liver disease (8.5 vs 4.4%), suggesting that the effect of cirrhosis on unbound clearance of nifedipine was even greater than on total clearance.

Large differences were also observed after oral administration of a controlled-release tablet containing 20 mg nifedipine. Absolute bioavailability was about 50% in the control subjects, with a range from 20 to 70%. A substantially greater bioavailability was determined in the patients with cirrhosis, particularly those with a shunt. Bioavailability ranged from 48 to 99% in patients that did not have a shunt, with a mean value of about 75%. Bioavailability was 100% in all 3 patients with a portacaval shunt. The large effects of a surgical por-

tacaval shunt on the pharmacokinetics and oral bioavailability of lidocaine, another drug subject to extensive first-pass metabolism after oral administration, has been reported by others.[74]

Gengo et al.[75] found that cirrhosis has similar effects on the pharmacokinetics of nimodipine, a recently approved calcium channel blocker. The apparent oral clearance was 217 ml/min in the patients and 519 ml/min in healthy control subjects. The patients with cirrhosis also showed a greater fall in MAP after a single dose of nimodipine than did the control subjects. A statistically significant relationship was demonstrated in most patients between MAP and nimodipine levels in plasma.

Nitrendipine is also a dihydropyridine that blocks calcium transport through vascular smooth muscle cells and antagonizes calcium-induced contraction. Dylewicz et al.[75] studied the pharmacokinetics of nitrendipine after an iv injection and repeated oral administrations in healthy subjects and in patients with liver disease (cirrhosis, chronic hepatitis, or acute hepatitis). The systemic clearance of nifedipine was reduced from 1290 ml/min in control subjects to 853 and 840 ml/min, respectively, in patients with either liver cirrhosis or chronic hepatitis. The systemic clearance of nitrendipine in patients with acute hepatitis was similar to the values found in control subjects.

On repeated oral administration of nitrendipine, 20 mg once daily, steady-state levels were about 3 times greater than control values in patients with cirrhosis, about 2 times greater in patients with chronic hepatitis, and about the same as controls in patients with acute hepatitis.

Buspirone is an anxiolytic agent, unrelated to benzodiazepines. Buspirone is well absorbed after oral administration but first-pass metabolism is so extensive that less than 10% of the dose is available to the systemic circulation. The pharmacokinetics of buspirone after a single oral dose was evaluated in patients with cirrhosis and in healthy human subjects.[77] The average peak concentration and total AUC were about 16 times higher in the patients than in the controls. Based on the pharmacokinetic evidence from this study, one must conclude that buspirone should be used cautiously in patients with liver disease.

As noted elsewhere in the text, the antiarrhythmic agent encainide when given to extensive metabolizers of debrisoquine undergoes extensive first-pass metabolism after oral dosing to form two active metabolites, O-desmethylencainide (ODE) and 3-methoxy-ODE. Bergstrand et al.[78] reported that patients with cirrhosis had a lower systemic clearance (by a factor of 2) and oral clearance (by a factor of 8) of encainide compared with values measured in control subjects, resulting in a threefold increase in oral bioavailability.

After a single oral dose of encainide or after repeated oral doses, encainide levels in plasma were much higher among the patients with cirrhosis. On the other hand, plasma levels of ODE and MODE in cirrhotics were comparable to those in healthy control subjects. The investigators concluded that although cirrhosis causes a large increase in steady-state levels of parent drug, a dosage adjustment is probably not required in patients with cirrhosis because no change occurs in the levels of the pharmacologically active metabolites.

The increase in bioavailability observed in patients with liver disease requires that oral doses of potent drugs with high hepatic extraction ratios be considered carefully for such patients and reduced when necessary.

Cholestasis

There are indications that cholestasis impairs the elimination of certain drugs. For example, the average half-life of rifampin was found to be 5.7 hr in patients with obstructive jaundice,[79] about twice as long as in patients without biliary obstruction. Other studies suggest that the elimination of meprobamate, pentobarbital, and tolbutamide may be altered in patients with certain forms of biliary stasis.[80] Studies with pancuronium, a neuromuscular blocking agent, in patients with total biliary obstruction indicate there is a doubling of half-life and a 50% decrease in the plasma clearance of the drug, compared to healthy subjects. Doses of pancuronium, beyond the initial dose, which may be required for prolonged surgery, should probably be reduced in such patients.[81]

Prediction of Disease Effects

Although liver dysfunction may have significant effects on the elimination of drugs, the degree of impairment of drug elimination in an individual being treated with a specific drug cannot be predicted. Unlike renal disease, for which creatinine clearance usually provides a quantitative index of the degree of impairment of drug excretion, indicators of impaired drug elimination are not apparent for hepatic disease. Although some correlations have been reported between certain biochemical

indices of hepatic function and parameters of drug elimination, currently available laboratory tests do not generally reflect, in a useful, quantitative, and predictive manner, the ability of the liver to metabolize drugs.

There is sufficient information to support the idea that measurement of drug kinetics can be used to provide quantitative information of hepatic function in patients with liver disease. There is also a theoretical basis to indicate that drugs can be used to define not only hepatic metabolic function, but also to describe abnormal splanchnic blood flow.[82,83] However, the relationship between the severity of the disease and the degree of impairment of elimination of a specific drug remains elusive.

There is hope that the elimination of certain drugs, like antipyrine, may serve as an index of the liver's ability to metabolize other drugs. Although some progress has been made in this direction, Farrell et al.[84] forecast only limited success. The observation in man that different microsomal enzyme systems are influenced to a different extent by liver disease indicates functional heterogeneity of the hepatic drug-metabolizing system and may limit general correlations between drugs.

Crom et al.[85] have evaluated a method to simultaneously assess three major processes involved in hepatic drug metabolism (glucuronide conjugation, hepatic blood flow, and microsomal oxidative metabolism) using a single cocktail containing three model substrates (lorazepam, ICG, and antipyrine). In a panel of healthy adult subjects, they found that mean oral clearances of the substrates were not different when the agents were given alone or together. The investigators suggest that "this simple technique . . . has potential applications in the assessment of developmental changes in hepatic drug clearance, as well as the effects of environmental, therapeutic, and pathophysiologic factors on three major processes involved in hepatic drug clearance."

The investigators then used this technique to evaluate the hepatic drug clearance status in children with leukemia before and after receiving remission-induction therapy.[86] The clearance of antipyrine increased by about 67% and that of lorazepam increased by about 50% after remission. There was no significant difference in ICG clearance before and after treatment.

Although there were no important differences in liver function test results before and after therapy, increases in the concentrations of albumin and apolipoprotein A in plasma, as well as a decrease in the levels of alpha$_1$-acid glycoprotein were noted. The investigators hypothesized that eradication of hepatic leukemic infiltration by acute lymphocytic leukemia remission therapy resulted in an improvement in microsomal metabolism of antipyrine and lorazepam.

More recently, Kawasaki et al.[87] measured the clearance of antipyrine, ICG, and galactose to evaluate changes in hepatic blood flow and hepatic drug metabolizing activity in patients with chronic liver disease. The clearance of galactose, like that of ICG, is related to hepatic blood flow. Galactose clearance decreased by about 30% and antipyrine and ICG clearance decreased by 60% and 85%, respectively, in patients with cirrhosis compared with healthy control subjects.

Clinical Significance

Questions regarding the clinical significance of the effects of liver dysfunction on drug elimination and, more specifically, whether or not the dosage regimen of a drug should be modified in a patient with liver disease are difficult ones to answer. Certainly, the incidence of adverse effects to drugs is expected to be higher in this population. Also, the accumulation of sedative and analgesic drugs in patients with liver disease increases the possibility of precipitating hepatic encephalopathy. An editorial on safe prescribing in liver disease in the British Medical Journal concludes that:[88]

> little change in prescribing is necessary when liver disease is inactive, though doses should be kept low and particular care should be taken with sedative and antidepressant drugs. When active liver disease or signs of hepatic decompensation are present, it is likely that drug metabolism is deranged, and the greatest care indeed should be exercised in prescribing.

A commentary on the effect of liver disease on the elimination of sedatives and analgesics notes that:[89]

> It would appear prudent to use such drugs cautiously in patients with parenchymal liver disease, titrating the dosage regimen in each patient to his clinical response, avoiding prolonged p.r.n. orders, and in selected instances monitoring of the drug plasma concentration.

A review of drug prescribing in hepatobiliary disease concludes with the following:[43]

> The best advice to the physician at this present state of knowledge is to administer drugs to patients with liver

disease carefully and to titrate the dose to the observed clinical response.

DISEASE EFFECTS ON DRUG BINDING

Drug distribution is significantly altered in certain diseases. Sometimes this is a result of changes in body composition (e.g., the accumulation of fluid), but far more often it results from changes in drug binding to plasma proteins. Changes in tissue binding are also likely, but our inability to measure these changes probably allows most to go undetected. Changes in drug binding and distribution are often accompanied by changes in drug elimination. The clearance of many drugs is a function of the free (unbound) fraction in plasma. The half-life of most drugs depends strongly on tissue binding and, to a lesser extent, on plasma protein binding. Relatively small changes in drug binding can dramatically affect the pharmacokinetics of a drug.

Albumin is considered to be the most important binding protein in plasma for acid and neutral drugs. More recent work has made it clear that α_1-acid glycoprotein (AAG) is of prime importance in the plasma binding of many basic drugs.

Drug binding to albumin is impaired in patients with renal or hepatic disease. This impairment is a result of a decreased concentration of protein in plasma (i.e., hypoalbuminemia) and the accumulation of endogenous inhibitors that interfere with drug binding. α_1-Acid glycoprotein is an acute phase reactant; its concentration in plasma rises in inflammation, malignancy, and stress, and falls in hepatic disease, nephrotic syndrome, and malnutrition.[90] Drug binding to AAG increases or decreases with AAG concentration in plasma.

Albumin Binding

Renal Disease. Plasma protein binding of acid drugs, including sulfonamides, phenytoin, thyroxine, clofibrate, salicylate, barbiturates, diazoxide, phenylbutazone, warfarin, and furosemide is impaired in patients with poor renal function.[91] The degree of impaired binding is often related to the severity of the renal disease. In many patients, reduced binding is observed despite the fact that serum albumin concentration is in the normal range. Plasma protein binding of most basic drugs is about the same in patients with uremia and in patients with normal renal function.[91]

Impaired drug binding in patients with renal disease is believed to be the result of decreased serum albumin and accumulation of endogenous inhibitors that interfere with drug binding to albumin. Depner and Gulyassy found that treatment of uremic plasma with a resin improved drug binding, presumably by removing binding inhibitors.[92] They extracted a substance from the resin that, when added to plasma from human subjects with normal renal function, impaired drug binding. The binding inhibitor is believed to consist of relatively low molecular mass (1000 to 2000 daltons) peptides.[93]

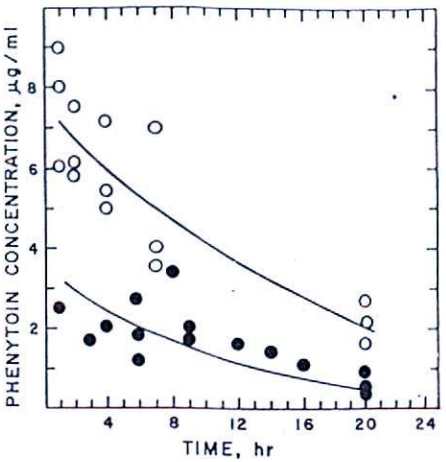

Fig. 13–7. Phenytoin concentrations in plasma of patients with uremia (●) or normal renal function (○) after a single 250-mg intravenous dose. (Data from Letteri, J.M., et al.[94])

The clearest consequence of impaired plasma protein binding is lower blood or plasma levels of drug in patients with impaired renal function. Figure 13–7 shows plasma levels of phenytoin after a single intravenous dose to patients with uremia and patients with normal renal function.[64] Typically, the fraction of total phenytoin concentration that is unbound in plasma is about twice as high in patients with poor renal function as it is in patients with normal renal function.

The plasma protein binding of warfarin and phenytoin was determined before and after kidney transplantation in patients with chronic renal disease.[95] Within 2 to 4 days after surgery, binding to plasma proteins increased dramatically and the free fraction of warfarin and phenytoin fell sharply, approaching values ordinarily seen in healthy control subjects, within two weeks of transplantation. Figure 13–8 shows the changes in serum creatinine and phenytoin binding after surgery.

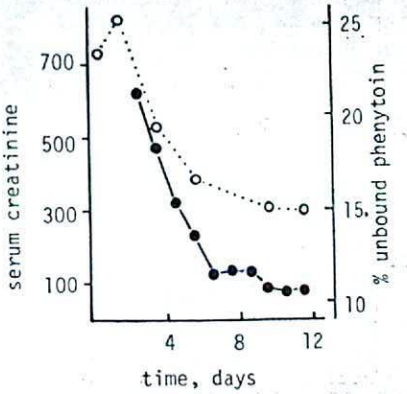

Fig. 13–8. Changes in serum creatinine levels (μmol/L) (●) and phenytoin binding (○) after a kidney transplant. (Data from Odar-Cederlof, S.[95])

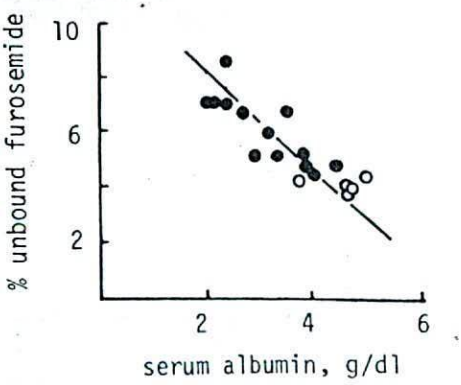

Fig. 13–10. Relationship between furosemide binding in plasma and serum albumin in normal subjects (○) and in patients with nephrotic syndrome or uremia (●). (Data from Rane, A., et al.[97])

Attention has also been given to the plasma protein binding of valproic acid and furosemide in patients with renal disease. At therapeutic plasma concentrations, unbound valproic acid was 8.4% in plasma of healthy subjects, but about 20% in patients with significant impairment of renal function.[96] Significant correlations were found in patients with renal disease between unbound valproic acid and serum creatinine, creatinine clearance, blood nitrogen, and blood uric acid (Fig. 13–9).

Rane and co-workers determined that the percent unbound furosemide in plasma was 36% higher in uremic patients and 65% higher in patients with nephrotic syndrome than in healthy control subjects.[97] When the data for the three study groups were combined, furosemide binding correlated with serum albumin concentration (Fig. 13–10).

Unlike several other basic drugs, the binding of diazepam is impaired in patients with renal disease.

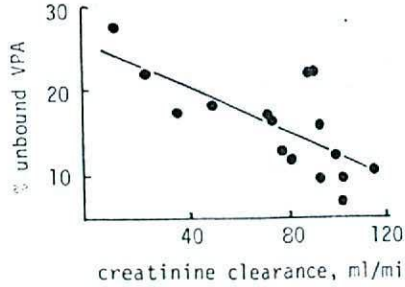

Fig. 13–9. Relationship between valproic acid (VPA) binding in plasma and renal function. (Data from Gugler, R., and Mueller, G.[96])

Kobe and associates reported that unbound diazepam in plasma was 1.2% in healthy subjects and 4.7% in uremic subjects.[98] Grossman and coworkers[99] reported that about a doubling of the free fraction of diazepam in plasma occurs in patients with uremic or nephrotic syndrome compared to healthy control subjects. Despite its basic character, diazepam is largely bound to serum albumin rather than to AAG.

Liver Disease. Impaired plasma protein binding of drugs is often observed in patients with liver disease. The prevalent mechanism responsible for changes in binding in hepatic disease is reduced serum albumin concentration, but accumulation of endogenous biochemicals, such as bilirubin, also occurs and may contribute to the reduced binding. A review of protein binding and kinetics of drugs in liver disease was presented by Blaschke.[100]

One report found that the plasma protein binding of diazepam and tolbutamide was reduced in patients with alcoholic cirrhosis; free fraction in plasma was 50 to 150% higher in cirrhotic patients than in healthy subjects.[101] The binding of both drugs was dependent on serum albumin concentration. Another report indicated that unbound tolbutamide was about 30% higher during the acute phase of viral hepatitis than after clinical recovery.[102] Changes in binding were the result, in part, of elevated bilirubin levels.

Brodie and Boobis compared the binding of salicylate, sulfadiazine, and phenylbutazone in serum of patients with alcohol-induced liver disease to that in serum of chronic alcoholics with no evi-

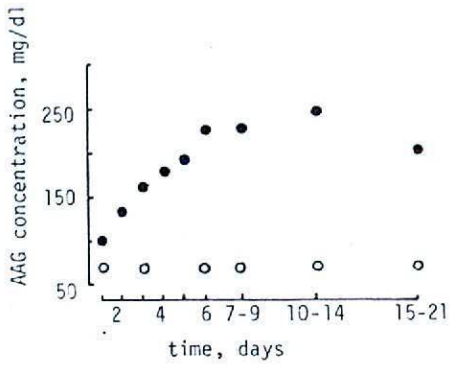

Fig. 13–11. α_1-Acid glycoprotein (AAG) concentrations in trauma patients after injury (●) and in healthy subjects (○) during a similar period of time. (Data from Edwards, D.J., et al.[111])

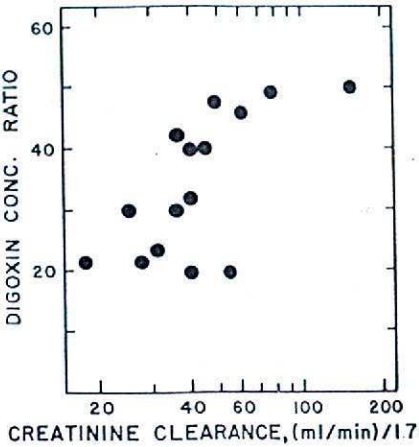

Fig. 13–12. Relationship between the myocardium-to-serum digoxin concentration ratio at necropsy and estimated antemortem renal function in individual patients. (Data from Jusko, W.J., and Weintraub, M.[112])

dence of liver disease.[103] Drug binding was normal in the chronic alcoholics but uniformly impaired in patients with alcoholic liver diseases.

Other investigators have reported decreased plasma protein binding of valproic acid[104] and furosemide[105] in patients with cirrhosis. In patients with liver disease, variations of the free fraction of valproic acid are correlated to albumin and bilirubin concentrations in serum.[104]

α_1-Acid Glycoprotein Binding

The variation in plasma albumin concentration as a result of disease is relatively narrow and is almost always in the direction of decreased concentrations. α_1-Acid glycoprotein (AAG) levels in plasma, on the other hand, show large fluctuations as a result of physiologic and pathologic changes. Decreases and increases in AAG concentrations have been observed, and parallel changes in the plasma binding of basic drugs have been reported.[106]

Quinidine binding in plasma increases shortly after gastric surgery in parallel with increases in the concentration of acute phase proteins including AAG.[107] Plasma protein binding of propranolol and chlorpromazine is increased in patients with inflammatory disease, specifically arthritis and Crohn's disease, consistent with a twofold increase in AAG concentrations, compared to control subjects.[108] Propranolol binding is also increased following myocardial infarction.[109]

Plasma AAG concentrations are considerably higher in patients with epilepsy than in age- and sex-matched control subjects (103 mg/dl vs 64 mg/dl); the binding of lidocaine is also greater in epileptics than in control subjects.[110] Lidocaine binding is also markedly increased in trauma patients, who manifest considerable elevations in AAG levels for several weeks after injury (Fig. 13–11).[111]

Tissue Binding

Since renal and hepatic diseases decrease the ability of plasma proteins to bind certain drugs because of the accumulation of endogenous binding inhibitors, one might expect a similar impairment of drug binding to other tissues in the body. With few exceptions, there is little information on this point.

Digoxin concentrations in serum and left ventricular tissues were measured at autopsy and related to estimated antemortem creatinine clearance in 15 patients.[112] A significant correlation was found between myocardium-to-serum concentration ratios of digoxin and creatinine clearance (Fig. 13–12). The uptake of digoxin by the myocardium was substantially reduced in patients with poor renal function.

Pharmacokinetic Implications

Changes in drug binding as a result of disease usually produce considerable change in the pharmacokinetic parameters of a drug. The most direct

change occurs in the apparent volume of distribution.

The relationship between drug binding and volume of distribution is given by the following equation:

$$V = V_B + (f_B V_T/f_T) \qquad (13\text{–}7)$$

where V is the apparent volume of distribution, V_B is blood volume, V_T is extravascular volume, and f_B and f_T are the free (unbound) fractions of drug in the blood and extravascular (tissue) spaces. A decrease in albumin binding, because of renal disease, hepatic disease, hypoalbuminemia, or for some other reason, leads to an increase in V. Disease-related increases in the concentration of acute phase proteins enhance the plasma binding of basic drugs and lead to a decrease in V. A decrease in tissue binding of a drug also results in a decreased volume of distribution.

The apparent volume of distribution of furosemide is about 50% larger in patients with nephrotic syndrome[97] and in patients with cirrhosis[105] than in healthy control subjects, largely as a result of decreased plasma protein binding. Increased plasma binding of propranolol[113] and quinidine[114] results in a decrease in volume of distribution. Consistent with a decrease in tissue binding, the apparent volume of distribution of digoxin is considerably smaller in patients with renal disease than in patients with normal renal function.[115]

The effect of plasma protein binding on drug clearance is less direct. The clearance (Cl) of a drug eliminated solely by hepatic metabolism is given by the following equation:

$$Cl = HBF \frac{f_B Cl_i}{HBF + f_B Cl_i} \qquad (13\text{–}8)$$

where HBF is hepatic blood flow rate, f_B is the fraction free in the blood, and Cl_i is the intrinsic clearance of drug by the liver. A similar expression can be developed for a drug subject only to renal excretion.

Whether or not changes in plasma protein binding affect clearance depends on the hepatic extraction ratio of the drug (i.e., the ratio of HBF to f_B Cl_i). For drugs with low hepatic extraction ratios, such as warfarin, phenytoin, or tolbutamide, HBF $\gg f_B$ Cl_i. Under these conditions, Equation 13–8 reduces to the following relationship:

$$Cl = f_B Cl_i \qquad (13\text{–}9)$$

Assuming no changes in a patient's intrinsic metabolizing ability, clearance of a low hepatic extraction ratio drug will be higher in a patient with impaired plasma protein binding than in a patient with normal binding capacity. As a consequence, steady-state levels of the drug will be lower in the patient with impaired binding capacity.

For example, the clearance of tolbutamide was 28 ml/min during the acute phase of viral hepatitis, but only 20 ml/min in recovery. The clearance of unbound tolbutamide was about the same during and after the acute phase, indicating that metabolism (elimination) was not impaired. The increased clearance of tolbutamide during the acute phase of the illness is a result of decreased plasma protein binding (i.e., an increase in f_B).[102]

For drugs with a high hepatic extraction ratio, such as propranolol, imipramine, or meperidine, HBF $< f_B$ Cl_i. Under these conditions, Equation 13–8 reduces to the following:

$$Cl \simeq HBF \qquad (13\text{–}10)$$

Theory predicts that the clearance of drugs with high extraction ratios will be largely independent of plasma protein binding. Kornhauser and coworkers showed that propranolol clearance is independent of drug binding over a twofold range of free fraction values in blood.[116] Steady-state concentrations of high extraction ratio drugs should be similar in patients with altered drug binding capacity and in patients with normal binding capacity.

The effect of changes in binding on the half-life of a drug is difficult to predict, because half-life is a function of both volume of distribution and clearance. Half-lives of low hepatic extraction ratio drugs are likely to be sensitive to changes in plasma protein binding, because of the dependence of clearance on free fraction in the blood. The half-life of phenytoin in uremic patients is much shorter than in healthy subjects;[117] the half-life of diazepam was 37 hr in renal failure patients, compared to 92 hr in healthy control subjects.[118] The shorter half-life of phenytoin or diazepam in patients with renal disease is the result of decreased plasma protein binding and increased clearance.

Half-lives of high extraction ratio drugs are also sensitive to changes in plasma binding, because of the effects of binding on apparent volume of distribution. An increase in drug binding to plasma proteins leads to a smaller volume of distribution and a shorter half-life; a decrease in drug binding leads to a larger volume of distribution and a longer half-life. As the binding of propranolol increases

from 90% (f_B = 0.10) to 95% (f_B = 0.05), the half-life of the drug decreases from 3.6 to 2.1 hr; over this range of drug binding the apparent volume of distribution decreases from 315 to 196 L.[119] As noted above, the clearance of propranolol is essentially independent of binding.

Changes in drug binding to tissues affects volume of distribution but not drug clearance. Therefore, a decrease in tissue binding leads to a decrease in volume of distribution and half-life; an increase in tissue binding leads to an increase in volume of distribution and half-life.

Clinical Significance

The pharmacokinetic consequences of changes in drug binding have been thoroughly explored, both theoretically and experimentally. The clinical implications of these changes in pharmacokinetics, if any, require further elaboration.

Changes in apparent volume of distribution may require changes in the loading dose of certain drugs given to patients with impaired drug binding. Particular attention has been given to the decreased volume of distribution of digoxin in patients with renal disease.[115] Ohnhaus and associates have recommended that the usual loading of digoxin (1.25 mg) be cut in half when digitalizing patients with severe renal failure.[120]

Much attention has been given to the clinical significance of the effects of altered binding on drug clearance and steady-state concentrations. Assuming no change in the patient's eliminating ability, the steady-state concentration of a drug with a low hepatic extraction ratio will be reduced in a patient with impaired plasma binding relative to the steady-state level in a patient with normal drug binding capacity.

On the other hand, steady-state levels of a drug with a high hepatic extraction ratio will be the same in patients with normal or impaired plasma protein binding. Does this mean that we should increase the dose of a low extraction ratio, largely metabolized drug in uremic patients to attain steady-state levels comparable to those in patients with normal plasma binding, or that we should not be concerned with binding changes for drugs with high hepatic extraction ratios? The answers to these questions are not easy to come by; we must rely on theory and limited clinical experience.

Theory, albeit with limited experimental support, suggests that drug effects will be more closely related to free (unbound) rather than total concentrations of drug in the blood or plasma. Accordingly, it is pertinent to examine concentrations of free drug at steady state in patients with impaired plasma binding.

Total drug concentration at steady state (C_{ss}) is given by the following expression:

$$C_{ss} = k_o/Cl \qquad (13\text{–}11)$$

where k_o is dosing rate (mg/min, mg/hr, or mg/day) and Cl is drug clearance. Free drug concentration ($C_{F,ss}$) is the product of free fraction in the blood and total drug concentration. Therefore:

$$C_{F,ss} = f_B\, k_o/Cl \qquad (13\text{–}12)$$

For drugs with low hepatic extraction ratios, eliminated solely by hepatic metabolism, clearance is given by Equation 13–9. Consequently:

$$C_{F,ss} = f_B\, k_o/f_B\, Cl_i = k_o/Cl_i \qquad (13\text{–}13)$$

Equation 13–13 indicates that free concentration at steady state for a drug with a low extraction ratio will be independent of changes in plasma protein binding. If this is the case, we should administer the same daily dose to patients with normal or impaired plasma binding and recognize that although total drug levels will be lower in the patients with impaired binding, free drug levels will be the same in both groups and so presumably will clinical effects.

Experimental support for this theory can be found in a study where phenytoin and clofibrate were given to healthy subjects and to patients with moderate hypoalbuminemia (plasma albumin of 1.2 to 3.9 g/dl), secondary to the nephrotic syndrome, but with relatively unimpaired renal function (creatinine clearance of > 50 ml/min) and with no evidence of liver disease.[121]

The percentage of unbound phenytoin in patients with the nephrotic syndrome was about twice that in control subjects (19.2% vs 10.1%). A strong linear correlation was observed between the free fraction of phenytoin and albumin concentration. Impaired binding was accompanied by a lower steady-state plasma concentration of phenytoin (2.9 μg/ml vs 6.8 μg/ml) because of an increase in the total clearance of the drug (0.8 ml/min per kg vs 0.37 ml/min per kg) in the nephrotic patient. The net effect however was *no significant difference* between the steady-state plasma concentration of free (unbound) phenytoin in healthy subjects (0.69 μg/ml) and that in patients with the nephrotic syndrome (0.59 μg/ml).

Similar results were obtained with clofibrate. Although binding was impaired (11.2% unbound vs 3.6% unbound) and steady-state plasma levels were reduced (46 μg/ml vs 131 μg/ml) in nephrotics compared to controls, the steady-state plasma concentrations of free (unbound) clofibrate were similar in healthy individuals (4.7 μg/ml) and in patients with nephrosis (5.1 μg/ml).

Gugler and associates recommend that, because the steady-state concentration of unbound drug in nephrotic patients is not different from that in subjects with normal plasma binding, the daily dose of drugs like phenytoin or clofibrate need not be changed for nephrotics.[121] This suggestion is important because it applies, in principle, to many drugs (compounds with low hepatic extraction ratios) under conditions of impaired plasma binding resulting from disease or drug-drug interactions.

The lower levels of some drugs in blood or plasma of patients with impaired plasma binding have important implications when therapeutic drug level monitoring is used. One must remember that a recommended therapeutic concentration range for a drug is based on the assumption of a certain degree of plasma protein binding. For drugs with low extraction ratios, a change in plasma binding usually means a change in therapeutic concentration range. For example, although the usual therapeutic concentration range for phenytoin in epileptic patients is 10 to 20 μg/ml, the therapeutic concentration range for an epileptic with severe renal failure, who has twice the free fraction of drug in plasma than the usual patient, is more likely to be 5 to 10 μg/ml. A less than adequate blood level of total drug may mean the patient requires a higher daily dose, but it may also mean that the patient is being adequately dosed but binds the drug less efficiently in plasma and does not need a change in dose.

The principles developed for phenytoin, clofibrate, and related drugs do not apply to drugs with a high hepatic extraction ratio. The clearance of these drugs approximates hepatic blood flow (HBF) and is independent of binding. Free drug concentration at steady state is given by the following equation:

$$C_{F,ss} = f_B\, k_o/HBF \qquad (13\text{–}14)$$

At a given dosing rate (k_o), total drug levels at steady state of a drug like propranolol or imipramine will be independent of a patient's plasma binding capacity, but free drug levels will be higher in a patient with impaired binding and lower in a patient with elevated binding. The steady-state concentration of a drug with a high hepatic extraction ratio may be more toxic or less effective in some patients than others depending on the patient's binding status.

The consequences of binding changes for propranolol or drugs with similar characteristics are of greater theoretical than clinical interest, because clinical problems have not been reported. This situation may relate to the fact that many of these drugs have a comfortable safety margin, that many of these drugs bind predominantly to AAG, the concentration of which is more likely to be elevated (greater binding) than reduced (less binding) in disease states, or that fluctuations in AAG concentration tend to be transient.

There is far more concern about drug usage in patients with hypoalbuminemia. In a comprehensive drug monitoring program, adverse reactions to phenytoin were recorded in 11.4% of 88 patients with serum albumin lower than 3 g/100 ml but in only 3.8% of 234 patients with a normal serum albumin.[122]

Surveillance of 240 medical inpatients receiving prednisone revealed a correlation between the frequency of side effects and serum albumin.[123] When serum albumin concentration was less than 2.5 g/dl, the frequency of prednisone side effects was doubled.

Of 6673 hospitalized medical patients monitored in a drug surveillance program, 1037 (15.5%) received chlordiazepoxide and 1202 (18.0%) received diazepam. Unwanted central nervous system (CNS) depression was noted in 7.1% of all diazepam recipients, but ranged from 2.9% in patients with normal serum albumin (> 4 g/dl) to 9.3% in those with hypoalbuminemia (< 3 g/dl). A similar trend was evident in patients receiving chlordiazepoxide.[124]

One reason for the higher rate of adverse drug effects in patients with hypoalbuminemia is that these patients may have had impaired elimination, in addition to reduced plasma protein binding. A reduced hepatic and/or renal function in conjunction with low serum albumin could cause increases in the steady state plasma concentrations of unbound drug with little or no change in total drug levels. In fact, the adverse reactions study with phenytoin includes all hypoalbuminemic patients without regard for the underlying disease.[122]

A more subtle pharmacokinetic reason for a

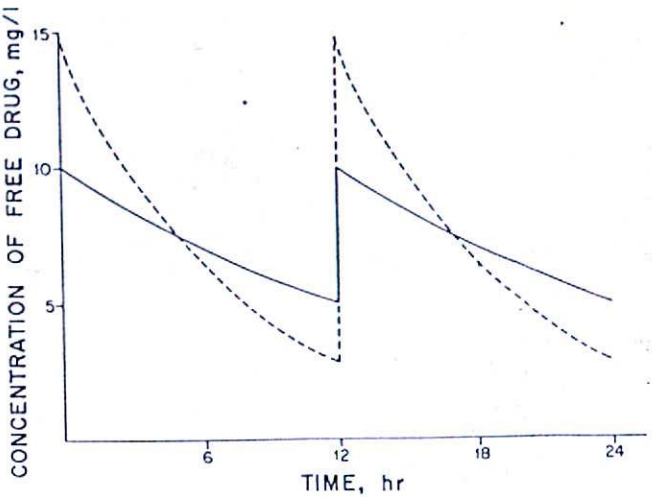

Fig. 13–13. Effects of a change in fraction unbound (f) on free drug concentration in plasma at steady state when a 100 mg/kg dose is given intravenously every 12 hr. Continuous line: f = 0.01, apparent volume of distribution (V) = 0.2 L/kg, $t_{1/2}$ = 12 hr. Stippled line: f increases to 0.03, V increases to 0.25 L/kg, and $t_{1/2}$ decreases to 5 hr. (Data from Levy, G.[125])

higher incidence of adverse drug effects in patients with reduced plasma binding relates to the fact that although the clearance of unbound drug is often unchanged, the half-life of the drug is usually shorter. If a patient with impaired plasma binding is treated with the usual dosage regimen, the same average free drug concentration is found as that in patients with normal plasma binding, but a higher peak concentration is also found (Fig. 13–13).[125]

The steady-state peak-to-trough concentration ratio for unbound phenytoin is only 1.25 in healthy subjects, but doubles in nephrotic patients with hypoalbuminemia and reduced plasma protein binding.[126] Although theory and usage suggest no change in the total daily dose of drugs such as phenytoin, diazepam, or clofibrate for patients with reduced plasma binding, more frequent dosing of these drugs may be advisable.

CARDIOVASCULAR DISEASE

The influence of heart disease on drug pharmacokinetics has been reviewed by Williams and Benet.[127] A more recent review, concerned specifically with congestive heart failure, is also available.[128] According to Equation 13–8, plasma clearance is determined by the intrinsic clearance of the eliminating organ, blood flow to that organ, and plasma protein binding. Cardiovascular disease can alter one or more of these variables.

Decreased hepatic perfusion is usually found in patients with congestive heart failure because of reduced cardiac output. These changes reduce the clearance of propranolol, pentazocine, lidocaine, and related drugs highly extracted by the liver.

Changes in cardiac function may alter the concentrations of drug-binding proteins like AAG, alter blood or fluid pH, or result in the production of endogenous binding inhibitors. These effects could influence drug binding in plasma or tissues.

Congestive heart failure (CHF) also affects drug metabolism but the basis for this is not clear. Hepner and associates studied the elimination of aminopyrine, a model drug that, like antipyrine, has a low hepatic extraction ratio and is eliminated only by oxidative metabolism in the liver, in patients with congestive heart failure and in control patients.[129] Aminopyrine clearance was 30 ml/min in patients with CHF and 125 ml/min in control patients. Recovery of labeled carbon dioxide, a by-product of aminopyrine metabolism, in the breath was markedly decreased in CHF patients. Impaired drug metabolism in CHF has also been observed with other drugs.

Lidocaine. The elimination of lidocaine is sensitive to changes in HBF. Figure 13–14 shows lidocaine concentrations in the plasma during intravenous infusion of 1 mg/min to patients with acute myocardial infarction, but with minimal cir-

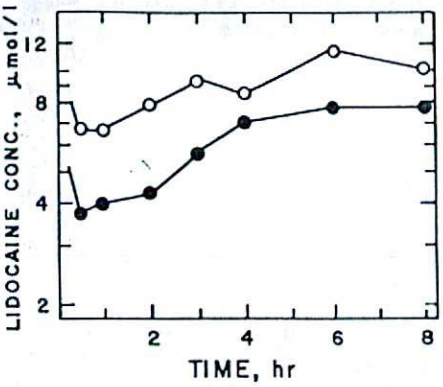

Fig. 13–14. Lidocaine concentrations in plasma after a loading dose and during a 1 mg/min intravenous infusion in patients with minimum circulatory disturbance and normal hepatic function (●) and in cardiothoracic surgical patients with overt circulatory disturbance and hepatic dysfunction (○). (Data from Aps, C., et al.[125])

culatory disturbance and normal hepatic function, and to cardiothoracic surgical patients with overt circulatory disturbance, including low cardiac output and hepatic dysfunction. Lidocaine levels are about 50% higher in the group with altered hemodynamics.[130] Similar findings have been reported by Prescott and co-workers.[131]

Other studies show a marked dependency of steady-state lidocaine levels on both cardiac index[132,133] and estimated HBF.[133] A nomogram has been developed for estimating the infusion rate of lidocaine necessary to attain a desired plateau concentration when cardiac output is known.[132] According to this method, a patient with a normal cardiac output of 80 ml/min per kg would require an infusion rate of 28 μg/kg per min (or about 2 mg/min for a 70-kg individual) to obtain a lidocaine concentration of 3 μg/ml. To achieve the same level in a patient with heart failure and a cardiac output of only 40 ml/min per kg requires a lidocaine infusion of 12 μg/kg per min (or about 0.8 mg/min for a 70-kg individual). The substantial decrease in lidocaine clearance in patients with reduced cardiac output makes it necessary to reduce the dose to avoid toxicity.

Propranolol. The elimination of propranolol, metoprolol, and several other β-blockers is dependent on HBF. These drugs are widely used to treat hypertension. Borderline hypertension patients often have high cardiac outputs, whereas permanent hypertension patients exhibit normal or reduced cardiac output. Weis and co-workers reported that propranolol clearance in permanent hypertension patients (cardiac output of 83 ml/min per kg) was only 50% of that observed in borderline hypertension patients (cardiac output of 111 ml/min per kg).[134]

Quinidine and Other Oral Antiarrhythmic Agents. Oral quinidine has been used for many years in the treatment of cardiac arrhythmias. In cardiac patients, about 20% of a dose is eliminated by renal excretion. Assuming the balance of the dose is metabolized in the liver, the hepatic extraction ratio of quinidine is about 0.20 to 0.25. The pharmacokinetics of quinidine were determined after intravenous administration to cardiac patients with and without CHF.[135] The half-life of quinidine was about the same in each group (6 to 7 hr), but renal clearance was about 50% smaller and total clearance about 35% smaller in CHF patients than in control cardiac patients, suggesting the need for a smaller maintenance dose of quinidine in patients with CHF. A particularly pronounced change in apparent volume of distribution of quinidine was noted; $V = 1.8$ L/kg for CHF patients and $V = 2.7$ L/kg for control subjects. The smaller V in patients with CHF suggests either enhanced plasma binding, possibly related to elevated levels of acute phase proteins, or impaired tissue binding.

Woosley[136] has summarized a large number of studies concerned with the pharmacokinetics and pharmacodynamics of lidocaine, quinidine, and other antiarrhythmic agents in patients with congestive heart failure. He observed that "changes in the pharmacokinetics of antiarrhythmic agents may be anticipated in patients with congestive heart failure (CHF), although the magnitude or direction of change is not always predictable."

Volume distribution may be as much as 50% smaller in patients with CHF and iv loading doses should be decreased proportionately. Decreased blood flow to the liver and kidneys and decreased hepatic drug metabolizing enzyme activity may seriously compromise the elimination of an antiarrhythmic drug.

Woosley stresses the fact that although it is widely assumed that antiarrhythmic therapy can benefit patients with highly symptomatic arrhythmias, "the pharmacokinetics of antiarrhythmic agents are made more variable and less predictable by heart failure, and the risk of toxicity is much greater than in patients with uncompromised car-

diac function." He concludes by pointing out that "therapy for patients with CHF should be initiated with low doses of the agent selected and the dosage carefully titrated while the patient is monitored to confirm both the efficacy and the absence of adverse effects."

Prazosin. Prazosin is an antihypertensive agent that may be useful in CHF because of its vasodilatory effects. After oral administration of a 5-mg oral dose, the total area under the blood level versus time curve was about twice as large in patients with CHF than in healthy subjects; the half-life of prazosin was 6 hr in CHF patients and 2.5 hr in control subjects.[137] Similar findings were reported in a later study.[138] The results suggest impaired metabolism of prazosin in patients with CHF and, possibly, the need for smaller doses.

Theophylline. Reduced theophylline clearance and increased toxicity have been reported in patients with CHF.[139] Powell and co-workers report a theophylline clearance of 26.5 ml/hr per kg in patients with CHF compared to values of either 55 ml/hr per kg (smokers) or 39 ml/hr per kg (non-smokers) in patients with uncomplicated asthma or chronic bronchitis.[140] Theophylline maintenance doses in patients with CHF must be reduced by about 50% to avoid adverse effects.

ACE Inhibitors. Angiotensin converting enzyme inhibitors have become mainline drugs in the treatment of congestive heart failure. Dickstein et al.[141] evaluated the pharmacokinetics of enalapril and enalaprilat after iv and oral administration of the parent drug and after iv administration of the active metabolite, in patients with stable, chronic CHF.

After oral administration of enalapril to these patients, the extent of absorption and the degree of conversion to enalaprilat were similar to values found in healthy control subjects, but absorption and hydrolysis were slower in patients with CHF. Peak levels of enalaprilat occurred about 2 hr later than expected and were about 30% higher than those found in control subjects. Enalaprilat concentrations were also consistently higher in CHF patients following iv administration of either enalapril or enalaprilat. Dickstein concluded that "the presence of CHF does not appreciably alter the pharmacokinetic behaviour of enalapril."

Loop Diuretics. Furosemide and bumetanide block active sodium chloride transport in the ascending limb of Henle's loop and have a much greater diuretic effect than the thiazides. They are widely used in the treatment of CHF, particularly in patients with pulmonary edema and in those who do not respond to thiazides.

The management of CHF is sometimes complicated by the failure of oral therapy to produce an effective diuresis and the need for iv administration to achieve the desired clinical response. Determinants of the diuretic response to furosemide are the total amount of drug delivered to the kidneys, the time course of that delivery, and the 'dose'-response or, more accurately, the urinary excretion rate-response relationship.

Oral furosemide has a bioavailability in healthy subjects of only 40 to 50%. Accordingly, more drug is needed to reach the same peak urinary excretion rate after oral administration than after iv injection. Furthermore, patients with CHF often show a shift in the dose-response relationship when compared with healthy subjects; a higher excretion rate of furosemide is required to produce the same sodium excretion rate. This resistance has been noted after both oral and iv administration.

Taking these factors into account still does not explain the very high resistance to oral furosemide in some patients with CHF. Some believe that the mechanism of this resistance is related to poor absorption of furosemide.

Brater et al.[142] studied the kinetics and dynamics of oral bumetanide and furosemide in patients with stable, compensated CHF and in healthy subjects. The mean time to reach peak concentration after a single dose was delayed in patients with CHF by 49 min for bumetanide and by 97 min for furosemide. Peak urinary excretion was 60% lower with bumetanide and 50% lower with furosemide in patients with CHF than in control subjects.

Only 23% of the oral dose of bumetanide was recovered in the urine in the patients compared with 30% in the controls; corresponding values for furosemide were 14 and 22%. The reason for the lower urinary recovery of unchanged drug in patients with CHF might be assigned to a change in the extent of absorption but the investigators concluded that the decreased recovery reflects renal impairment in patients with CHF rather than reduced bioavailability.

Bumetanide and furosemide appear to be absorbed more slowly in patients with CHF than in normal subjects. With furosemide there was a doubling of the time to peak urinary excretion rate. This delay was associated with a 50% decrease in peak urinary excretion rate, indicating not only a

lag in absorption, but a decreased absorption rate as well.

Brater et al. suggested that "because the time course of delivery of any drug to the active site is an important determinant of overall response . . . , it is conceivable that this change in time course, but not extent, of absorption could in part be responsible for the diminished response to oral diuretics so often observed clinically in patients with CHF and other edematous disorders. The delayed rate of absorption might render excretion rates of diuretic attained in the urine sufficiently low to blunt overall response."

More recently, Vasko et al.[143] also studied the absorption of furosemide in patients with CHF who were receiving their usual oral dose of the loop diuretic. Each patient was evaluated twice, once while decompensated and again after attaining normal weight and while clinically compensated.

Most patients showed a substantially different serum level-time profile on the two occasions, with a considerable decrease in the time to peak drug concentration and a higher peak concentration when dry weight was achieved. The relative bioavailability of furosemide also tended to be larger in compensated patients than in decompensated patients but the difference was not statistically significant.

These findings indicate that the absorption of furosemide in patients with CHF improves as a patient's clinical status is upgraded, suggesting that the disease process in some way alters absorption. The principal changes in gastrointestinal physiology that have been noted in CHF are delayed gastric emptying, decreased GI motility, altered transit times, edema of intestinal epithelium, and decreased splanchnic blood flow. Vasko et al. suggested that their "results reinforce the clinical impression of physicians that absorption of furosemide in patients with decompensated congestive heart failure is abnormal and a prompt diuretic response requires intravenous therapy."

THYROID DISEASE

When thyroid function is altered, there are a series of physiologic changes that may affect drug absorption, excretion, and metabolism. The influence of thyroid dysfunction on drug pharmacokinetics has been reviewed by Shenfield[144] and more recently by O'Connor and Feely.[145]

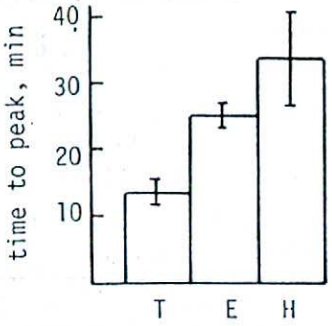

Fig. 13–15. Time-to-peak concentration after a single oral dose of acetaminophen in thyrotoxic (T) and hypothyroid (H) patients, and in the same patients when treated and euthyroid (E). (Data from Forfar, J.C., et al.[147])

Absorption

The bioavailability of riboflavin is increased in hypothyroidism and decreased in hyperthyroidism because of changes in gastrointestinal motility.[146] Enhanced absorption of riboflavin is also observed when gut motility is reduced by administration of an anticholinergic agent. Serum digoxin concentrations may be low in hyperthyroid patients because of hypermotility and decreased bioavailability.

Absorption of acetaminophen is faster in patients with untreated thyrotoxicosis than after treatment; the absorption of acetaminophen is relatively slow in hypothyroid patients (Fig. 13–15).[147] The absorption rates of propranolol and oxazepam are also increased in hyperthyroidism due to increased GI motility.[145]

Excretion

Renal plasma flow is reduced in hypothyroidism and increased in hyperthyroidism. The renal clearance of drugs may be affected in a similar way, but this is not firmly established. Most studies concerned with the effects of thyroid disease on renal clearance have examined digoxin elimination, but the results are conflicting.

There is considerable and controversial literature on cardiac glycosides and thyroid dysfunction. Clinically, hyperthyroid patients are less sensitive to these drugs. For many years, these differences were thought to be entirely pharmacologic in nature. In 1966, however, Doherty and Perkins reported their findings of relatively low blood levels of digoxin in hyperthyroid patients and relatively

high blood levels in hypothyroid patients, compared to control patients.[148]

The findings in hyperthyroid patients have been confirmed by several investigators;[149,150] the results in hypothyroid patients have been confirmed by some[149] but not by others.[150] The basis for these pharmacokinetic changes is unexplained; they could relate to changes in renal or biliary excretion or in hepatic metabolism. Shenfield believes that pharmacokinetic changes alone cannot explain the clinical resistance to digoxin in hyperthyroidism and proposes that resistance is related to an increased number of Na^+ K^+-ATPase pumps.[144] This hypothesis is consistent with findings in neonates who are also relatively resistant to the effects of digoxin.

Other studies have shown that hyperthyroidism has no effect on the renal clearance of atenolol and nadolol.[145]

Metabolism

In general, the activity of hepatic microsomal drug metabolizing enzymes is reduced in hypothyroidism and increased in hyperthyroidism. The half-life of antipyrine was found to be about 8 hr in hyperthyroid and 17 hr in hypothyroid patients.[151] After treatment, half-life values were about 12 hr in each group, well within the normal range. Similar findings have been reported for the elimination of methimazole and propylthiouracil, antithyroid agents, in hypo- and hyperthyroid patients.[152]

Forfar and co-workers report that differences in the absorption rate of acetaminophen in patients with thyroid disease are paralleled by differences in metabolic clearance.[147] Relative to euthyroid patients, hypothyroid patients absorb and eliminate acetaminophen more slowly, whereas hyperthyroid patients absorb and eliminate the drug more rapidly. The rates of glucuronidation of acetaminophen and oxazepam are increased in hyperthyroidism.[145]

Thyroid disease seems to have a considerable effect on the elimination of propranolol.[153] In hyperthyroid patients receiving 160 mg/day, steady-state levels of propranolol rose from 38 ng/ml when hyperthyroid to 75 ng/ml when euthyroid. In hypothyroid patients receiving the same dose, there was a substantial fall in steady-state propranolol concentrations following treatment with thyroxine, from 117 ng/ml to 69 ng/ml.

While oxidative metabolism of antipyrine, propranolol, metoprolol, and theophylline is enhanced in hyperthyroidism, the clearance of other drugs, including diazepam, warfarin, and phenytoin, is unchanged.[145]

INFLUENZA AND RELATED DISEASES

In 1978, Chang et al.[154] observed that the half-life of theophylline was prolonged during viral upper respiratory infection in children with chronic asthma. These findings were confirmed by Kraemer et al.[155] in 1982. Kraemer and his colleagues reported that during the 1980 influenza outbreak in King County, Washington, 11 children whose asthma had been well controlled with theophylline rapidly developed drug toxicity, with no change in dose, while suffering a bout of febrile viral illness. Toxicity included two cases of seizures. Theophylline concentrations in serum ranged from about 8 to 20 μg/ml before the viral illness and from 22 to 48 μg/ml during the illness, when the children were manifesting theophylline toxicity.

The apparent inhibition of theophylline metabolism during influenza may be related in part to the fever associated with the infection. Forsyth et al.[158] determined antipyrine clearance in saliva after a single oral dose to children ranging in age from 5 months to 5 years during a period of elevated body temperature (range 38.6° to 39.2°) secondary to upper or lower respiratory tract infection and again after the bout of fever.

Antipyrine clearance during the infection and fever was only about half that found during the control period. In an earlier study, Elin et al.[157] determined in adult subjects that etiocholanolone-induced fever also decreased the clearance of antipyrine compared to that observed during an afebrile control period, but the inhibition was less pronounced than that observed during natural fever in children.

The effects of viral infections on hepatic oxidative drug metabolism are believed to be mediated via the stimulation of interferon. A wide variety of interferon-inducing agents and interferon itself have been found to decrease hepatic concentrations of cytochrome P450-dependent drug metabolizing enzymes. Administration of influenza virus vaccine may also lead to elevated interferon levels, and several studies have demonstrated that flu vaccine depresses the metabolism of certain drugs subject to oxidative metabolism in the liver.[158,159]

Meredith et al.[160] studied the effects of influenza vaccine on the pharmacokinetics of intravenous chlordiazepoxide and lorazepam and oral theo-

phylline, after a single dose of each drug, in healthy male subjects. Each subject was studied with one of the drugs 5 days before and either 1 or 7 days after a standard dose of a trivalent flu vaccine released for 1982.

The vaccine inhibited the metabolism of theophylline but not that of chlordiazepoxide, which is also oxidized, nor that of lorazepam, which is glucuronidated. The first day after vaccination, the clearance of theophylline was reduced by about 25%, compared with baseline. Impaired metabolism was no longer evident on day 7.

Levels of alpha-interferon were elevated in 3 of the 7 subjects for at least 6 to 8 hr after vaccination but returned to baseline within 24 hr. Plasma levels of gamma-interferon were elevated in all subjects for about 4 days after vaccination.

Meredith et al. concluded that the inhibition of theophylline is small and transient, seemingly related to the stimulation of interferon by the vaccine, and appears to be greater in subjects with high prevaccination theophylline clearances. No reasons are obvious to explain the apparently selective effects of flu vaccine on theophylline but not on chlordiazepoxide metabolism.

Other investigators have failed to detect an effect of influenza vaccination on theophylline metabolism, and there is now reason to believe that whether or not theophylline metabolism is inhibited depends on the composition of the vaccine. Winstanley et al.[161] found no effect of a highly purified subunit influenza vaccination on steady-state levels of theophylline in healthy subjects or in patients with chronic obstructive bronchitis.

These investigators proposed that "an ideal [influenza vaccine] would contain only those proteins that induce a protective antibody response—principally haemagglutinin (HA) and neuraminidase (N). Disruption of whole viron . . . produces a mixture of HA, N, viral RNA, matrix protein, and viral and egg lipid. These latter substances, although not important contributors to the antibody response, are potent interferon inducing agents."

Winstanley et al. suggest that highly purified subunit influenza vaccines are safe when given to patients receiving theophylline, but less purified flu vaccines should still be used with caution in such patients.

Grabowski et al.[162] found that a split virus influenza vaccine produces no detectable interferon activity in serum and no production of interferon in tonsil or peripheral lymphocyte cultures. They concluded that patients being treated with theophylline who receive split virus influenza vaccine need no modification of their theophylline dose.

Despite assurances of the safety of more purified flu vaccines, caution may still be prudent for patients on relatively high-dose theophylline therapy. Because of the nonlinear characteristics of theophylline metabolism, a relatively modest decrease in theophylline clearance may produce disproportionately large increases in steady-state theophylline levels, particularly in patients with serum levels in the range of 15 to 20 μg/ml.

BURN INJURY

Extensive and severe burns induce a variety of physiologic changes that could produce unpredictable changes in the pharmacokinetics of drugs.[163] Some investigators have found elevated glomerular filtration rates after burn trauma. This may contribute to the unusually rapid renal excretion of aminoglycoside antibiotics in burn patients.

In 14 burn patients treated for serious gram-negative infections, the use of usual doses of gentamicin, up to 5 mg/kg per day, resulted in subtherapeutic plasma concentrations; peak gentamicin concentrations were consistently below 4 μg/ml.[164] Gentamicin half-life in these patients was unusually short, particularly in the younger burn patients. Satisfactory gentamicin levels were achieved by increasing the daily dose, to as high as 12 mg/kg per day in the younger patients, and decreasing the dosing interval from 8 to 4 hr.

A follow-up study in 66 burn patients generally confirmed these initial results.[165] About 75% of the patients required doses greater than the recommended dose to achieve adequate drug levels in the serum. Dosing intervals of every 4 hr were required in about 25% of the patients and of every 6 hr in about 40% of the patients.

Larger-than-average doses of vancomycin also seem to be needed in some patients with serious burns. Brater et al.[166] measured the clearance of vancomycin from serum in patients with burns and found that it correlated closely ($r = 0.93$) with creatinine clearance. Five of the 10 patients with burn injury had creatinine clearances greater than 120 ml/min; these values ranged from 142 to 192 ml/min. The five highest values of vancomycin clearance occurred in the same 5 patients; these values ranged from 108 to 215 ml/min. The investigators suggested that a reasonable therapeutic strategy in

a patient with burns would be to dose vancomycin based on the patient's creatinine clearance.

More recently, Garrelts and Peterie[167] determined vancomycin dosage requirements in patients with burns and medical/surgical patients with normal renal function who served as controls. The initial dosage regimen for most patients was 1.0 g vancomycin given iv every 12 hr. In each patient, however, the initial regimen was modified when necessary to achieve a peak serum level between 25 to 35 μg/ml and a trough level between 5 to 10 μg/ml.

The burn patients varied widely in the extent of total body surface area affected; estimates ranged from 4 to 46%, with a mean of 24%. Creatinine clearance was 131 ml/min in the patients with burns and 117 ml/min in the control patients. The difference was relatively small and not statistically significant. The average peak concentrations of vancomycin were 27 and 31 μg/ml in the burn and control groups, respectively. Mean trough levels were about 8 μg/ml in each group.

Despite the similarities between the two groups in age, weight, and creatinine clearance, burn patients required much larger doses of vancomycin to maintain serum levels comparable to control patients: 47 mg/kg/day versus 26 mg/kg/day. On average, patients with burn injuries required nearly 1 g/day more vancomycin than control patients.

Burn patients also had to be dosed more frequently than control patients to maintain trough levels within the specified range. Only 4 of 9 burn patients were dosed every 12 hr; the others needed doses every 8 hr or, in one case, every 6 hr. On the other hand, 7 of the 8 control patients could be given vancomycin every 12 hr and 1 patient received the drug every 18 hr.

Contrary to the results in the earlier study by Brater et al.,[166] Garrelts and Peterie concluded that the increased dosage requirement for vancomycin in patients with burns is not related to creatinine clearance. Accordingly, they believe that monitoring serum levels of vancomycin in patients with burn injuries is essential to avoid underdosing and therapeutic failure.

Acute stress ulceration of the stomach and duodenum is a life-threatening complication of burn injury. Attempts to control gastric acidity by iv administration of cimetidine have had mixed success. Martyn et al.[168,169] have considered the possibility that the usual dose of cimetidine may be ineffective in patients with burn injuries because of enhanced clearance and subtherapeutic blood levels.

Studies in adults showed that both creatinine clearance and cimetidine clearance were much larger in patients with burns than in matched control subjects.[168] Creatinine clearance was 172 ml/min in burn patients compared with a value of about 125 ml/min in controls. Total clearance of cimetidine was 14.0 ml/min/kg in the patients and 8.2 ml/min/kg in the controls.

Martyn et al. also studied cimetidine pharmacokinetics in children with burn injuries.[169] Age ranged from 4 months to 17 years, with a mean of 6 years. Mean cimetidine clearance in these patients was 16.2 ml/min/kg, slightly higher than the mean value found in adult patients with burns and about twice as high as the mean value found in adult control subjects. Endogenous creatinine clearance normalized to 70 kg was 190 ml/min in the children with burns, again slightly higher than in adult patients with burns and much higher than in adult controls. The correlation coefficient between creatinine and cimetidine clearance was 0.93. These results support the hypothesis that the higher dosage requirements of cimetidine in children with burn injuries is due, at least in part, to the increased clearance of cimetidine in such patients.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inherited disorder, characterized mainly by pancreatic insufficiency and progressive chronic lung disease. Evidence has been accumulating that suggests altered drug disposition in patients with CF. Specifically, there appears to be increased renal excretion of certain drugs and increased hepatic metabolism of others.

Knoppert et al.[169] studied theophylline metabolism following a single iv dose of aminophylline in young adults with stable, mild to moderate CF and in healthy control subjects of similar age. The total clearance of theophylline was 40 to 50% greater in patients with CF than in controls. The renal clearance of theophylline, which ordinarily accounts for about 10% of the total clearance, was increased by 45% and the nonrenal clearance by 41%, compared with control values.

The increased nonrenal clearance of theophylline in CF was the result of increased hepatic metabolism to each of its three main metabolites, 1-methyluric acid, 3-methylxanthine, and 1,3-dimethyluric acid. The formation clearances for each of

these metabolites increased by more than 50%. Also, the renal clearance of each metabolite was greater in subjects with CF than in control subjects.

The increased renal clearance of theophylline observed in this study is consistent with earlier reports of increased renal clearance of dicloxacillin, methacillin, and tobramycin in patients with CF. The increased metabolic clearance of theophylline is largely related to enhanced N-demethylation and ring hydroxylation activity in patients with CF. In summary, there may be a need for larger doses of theophylline and other drugs in patients with CF to achieve adequate response.

CONCLUSIONS

Much more needs to be learned about how to best use drugs in patients, particularly critically ill patients. Dosing guidelines can be developed for many drugs in certain disease states when the patient's condition is stable. Far more individual judgment and empiricism is required in the acutely ill patient, when hemodynamics and end-organ function may fluctuate mercurially or decline precipitously. One thing is certain, we must never make the assumption that the same dose of a drug is adequate for every patient who requires it.

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