The therapeutic consequence of induction can be appreciated from the difference in the response-time curves, shown in the bottom graph of Fig. 12–1. *Response* here is defined as the elevation in prothrombin time above a baseline value of 14 sec. The overall response, given by the area under the response-time curve after the single oral dose, is substantially reduced in the presence of rifampin. Consequently, one would expect under steady-state conditions that the dosage of warfarin must be increased in the presence of rifampin to maintain the same prothrombin time. The reason for the apparently poor correlation between response and plasma warfarin concentration during the first 48 hr after warfarin administration, when response is increasing and concentration is falling, is discussed in Chap. 23, Turnover Concepts.

Rifampin is a known inducer of hepatic drug metabolism, and the data provided in Fig. 12–1 are generally consistent with induction of warfarin metabolism by rifampin. However, there are problems with respect to the interpretation of these data, in addition to the above mentioned problem of relating warfarin concentration to response. Warfarin is marketed as a racemate. Its enantiomers have different anticoagulant potencies and different kinetic properties. Furthermore, the change in prothrombin time is a consequence of changes in several clotting factors. Racemates are commonly used today, instead of a pure enantiomer. One isomer may potentiate or inhibit the kinetics or dynamics of the other. As long as racemates are administered, kinetic and dynamic data on the pure enantiomers, while helpful to define mechanisms involved, are of questionable value without corresponding data following the racemate as well. Clearly, chirality is a major issue in therapeutics.

High Extraction Ratio. Induction of metabolism of a drug with a high hepatic extraction ratio has kinetic consequences very different from those of a drug with a low hepatic extraction ratio, as illustrated in Fig. 12–2. Pretreatment with the inducer pentobarbital appears to have little effect on the pharmacokinetics of alprenolol after its intravenous (i.v.) administration. Following oral administration, however, both the peak concentration (C_{max}) and *AUC* are dramatically reduced, although there is little apparent change in the half-life. These observations, at first glance, appear to be inconsistent. Knowing that this drug is metabolized only in the liver and on calculating (from dose and *AUC* following i.v. admin-

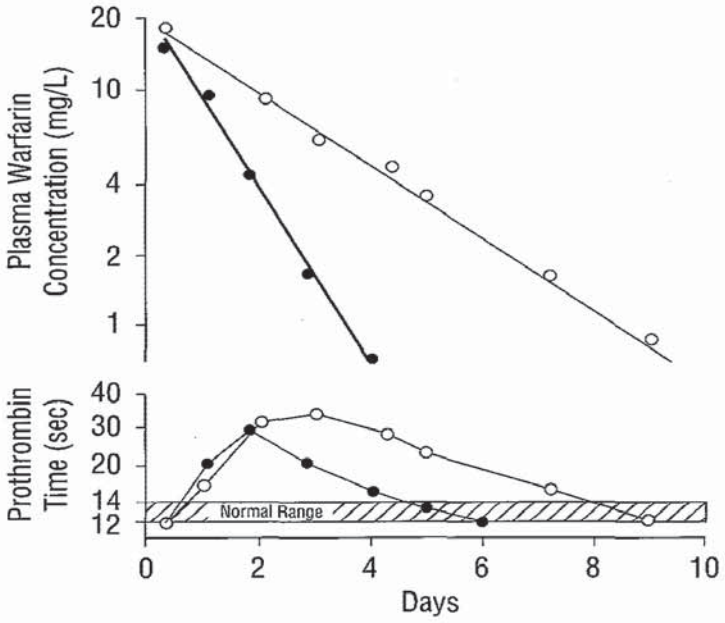

Fig. 12–1. The half-life of warfarin, a drug with a low extraction ratio, is shortened and clearance is increased when it is given (open circles) as a single dose (1.5 mg/kg) before (black line) and while (colored circles and line) the inducer, rifampin, is being administered as a 600-mg dose daily for 3 days prior to warfarin administration. The peak and duration of the elevation in the prothrombin time (response) are decreased when rifampin is coadministered (lower graph) (1 mg/L = 3.3 μM). (Reproduced, with permission, from O'Reilly, R.A.: Interaction of sodium warfarin and rifampin. Ann. Intern. Med., *81*:337–340, 1974.)

istration) a clearance of 1.2 L/min in this individual, an explanation can be offered. Pentobarbital induces alprenolol metabolism, which manifests itself as a decrease in alprenolol oral bioavailability. The argument for this conclusion follows.

The hepatic extraction ratio of alprenolol is high; its clearance approaches hepatic blood flow, approximately 1.35 L/min, and its oral bioavailability (F), calculated by comparing the dose-corrected AUC after oral and i.v. administrations, is 0.22. Given that the low bioavailability is due solely to hepatic extraction, the hepatic extraction ratio ($1 - F_H$) is 0.78. Bioavailability reflects the balance between perfusion, which forces drug through the organ, and enzymatic activity, which removes drug. After induction, which increases enzyme activity, oral bioavailability (based on comparison of AUC values) decreases to 0.06, almost a fourfold change, and hence the hepatic extraction ratio increases to 0.94. Because clearance is perfusion rate-limited and because there is no evidence in humans that pentobarbital alters hepatic blood flow, there is only a small increase in clearance. The increase in hepatic extraction ratio, and hence clearance, is only 20% (from 0.78 to 0.94). The lack of change in terminal half-life after induction also indicates that pentobarbital has no effect on the volume of distribution of alprenolol. Thus, induction of the metabolism of this drug, or any other drug with a high hepatic extraction ratio, has therapeutic implications when administered orally, but not when given intravenously. A larger oral dose, or more frequent administration, is needed in the presence of the inducer to produce the same effect, assuming all activity resides with the drug.

Alprenolol, like warfarin, is also administered as a racemate. With little difference in the kinetics of the isomers, the conclusions here for the mixture apply as well to each of the isomers. Indeed, if there are virtually no pharmacologic, toxicologic, or pharmacokinetic differences between the isomers, a benefit in using the racemate is that it does not incur the often considerable cost of separating the isomers.

Decreased Hepatocellular Activity

Examples of drugs that inhibit the metabolism of other drugs are given in Chap. 17, Interacting Drugs. Reduced metabolism can also be a consequence of hepatic disease (Chap. 16), dietary deficiencies, and other conditions. Whatever the cause of decreased metabolic activity, the kinetic consequences depend on the hepatic extraction ratio of the drug.

Low Extraction Ratio. The effect of decreasing hepatocellular activity for a drug of low hepatic extraction ratio is illustrated by data for chlorzoxazone and chlordiazepoxide.

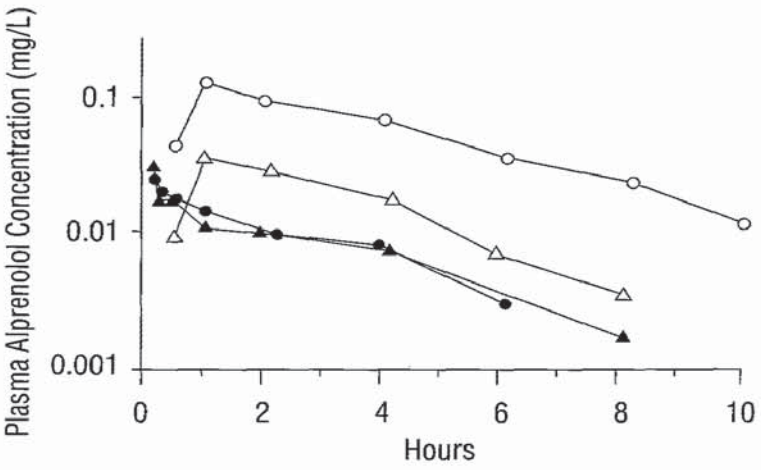

Fig. 12–2. Induction of alprenolol metabolism by pentobarbital treatment produces marked differences in the plasma concentration when the drug is given orally (200 mg), but not when given i.v. (5 mg). Alprenolol was administered before (black lines: ●, i.v.; ○, oral) and 10 days into (colored lines: ▲, i.v.; △, oral) a pentobarbital regimen of 100 mg at bedtime (1 mg/L = 4.0 μM) (From Alvan, G., Piafsky, K., Lind, M., and von Bahr, C.: Effect of pentobarbital on the disposition of alprenolol. Clin. Pharmacol. Ther., 22:316–321, 1977.)

The concentration-time profile of the muscle relaxant chlorzoxazone in a subject after a 750-mg oral dose is very different from that seen 10 hr after a single 500-mg oral dose of disulfiram (Fig. 12–3). The mean clearance and half-life values were 3.3 ml/min/kg and 1.2 hr in the absence and 0.5 ml/min/kg and 5.1 hr in the presence of disulfiram, a selective inhibitor of oxidative metabolism. The changing concentration of the inhibitor (and its metabolites following the single 500-mg dose) and the limited time of sampling in the presence of the inhibitor preclude being highly quantitative. Nonetheless, the effect of decreased hepatocellular activity is clear for a drug with a low extraction ratio; clearance decreases and half-life increases.

Another example is that of the anxiolytic drug chlordiazepoxide (Fig. 12–4). Its half-life is increased and its clearance is decreased in patients with hepatic cirrhosis. Oral bioavailability and volume of distribution (not shown) are unaffected.

That chlordiazepoxide has a low hepatic extraction ratio even in healthy subjects can be deduced from the data in the figure if one also knows that the drug is eliminated primarily

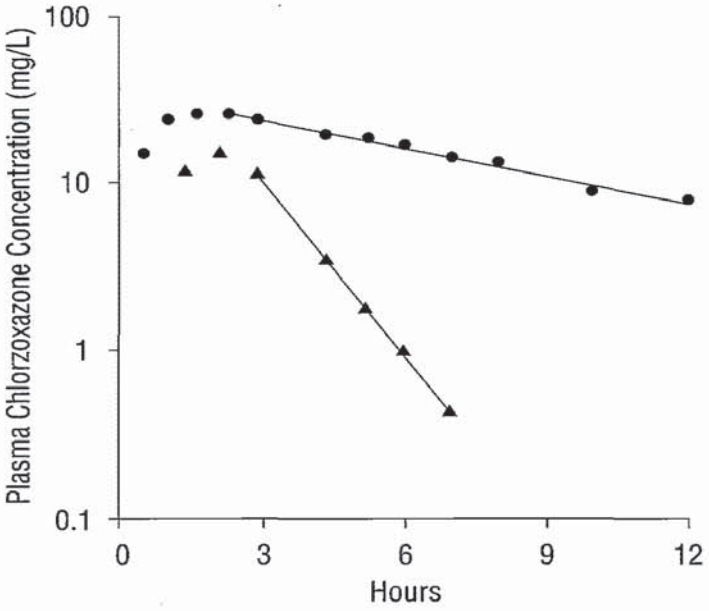

Fig. 12–3. The plasma concentration-time profile of chlorzoxazone after a single 750-mg oral dose (▲) is dramatically increased after disulfiram treatment (●). Disulfiram (500 mg orally) was given 10 hr before the chlorzoxazone. The increase in half-life and decrease in clearance are expected for a low extraction ratio drug when metabolic activity is decreased. (Redrawn from Kharasch, E.D., Thummel, K.E. Mhyre, J., and Lillibridge, J.H.: Single-dose disulfiram inhibition of chlorzoxazone metabolism: A clinical probe for P450 2E1. Clin. Pharmacol. Ther. 53:643–650, 1993. Reproduced with permission of C.V. Mosby.)

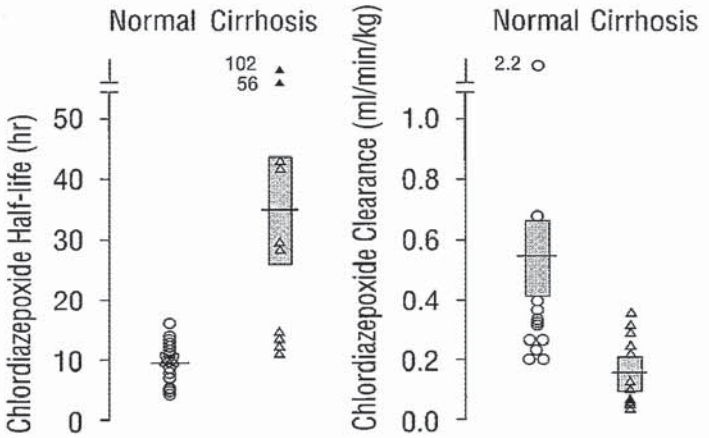

Fig. 12–4. Chlordiazepoxide's half-life is increased and total clearance is decreased in patients with hepatic cirrhosis compared to normal subjects. Mean (±SEM) and individual values are shown. (Redrawn from Sellers, E.M., Greenblatt, D.J., Giles, H.G., Naranjo, C.A., Kaplan, H., and MacLeod, S.M.: Chlordiazepoxide and oxazepam disposition in cirrhotics. Clin. Pharmacol. Ther., 26:240–246, 1979. Reproduced with permission of C.V. Mosby.)

by hepatic metabolism, the blood-plasma concentration ratio is close to 1.0, and average hepatic blood flow is 20 mL/min/kg. In subjects with normal hepatic function, the hepatic extraction ratio [CL_H/Q_H = (0.55 mL/min/kg)/(20 mL/min/kg)] is then expected to be only about 0.03 or less.

High Extraction Ratio. The kinetic consequences of inhibition of metabolism of a drug with a high hepatic extraction ratio are illustrated by the coadministration of cimetidine and labetolol (Fig. 12–5). That labetolol is a drug of high hepatic extraction ratio is deduced from its clearance, 1.06 L/hr (estimated by dividing the i.v. dose by the corresponding *AUC* given in the article), approaching hepatic blood flow and from the knowledge that labetolol is eliminated almost exclusively by hepatic metabolism. The i.v. dose of labetolol is much smaller than the oral dose, because the drug is highly extracted in the liver, and hence subject to extensive first-pass hepatic loss, and because the pharmacologic activity primarily resides with the drug, rather than with its metabolites.

There is a large increase in *AUC* for labetolol when administered orally, but not when given intravenously, in the presence of cimetidine. This observation is expected following inhibition of the elimination of a drug with a high hepatic extraction ratio. The lack of change in area following i.v. administration reflects the minor decrease caused by cimetidine in the hepatic extraction ratio and hence in clearance. Evidently, blood flow continues to limit the hepatic elimination of labetolol even when inhibition occurs. This would not be so if the degree of inhibition were such as to reduce labetolol to a drug of low hepatic extraction ratio. The large increase in *AUC* following oral administration is a consequence of increased bioavailability; here the increment is about 56%, while only a minor decrease (20%) was seen in the hepatic extraction ratio. The therapeutic corollary of the kinetic changes in the presence of cimetidine is heightened activity of labetolol when given orally, but not when given intravenously.

Altered Blood Flow

As presented in Chap. 11, changes in organ blood flow affect clearance only when extraction ratio is high. This conclusion is based on the concept of a perfusion-rate limitation. It should be borne in mind, however, that effects secondary to an altered blood flow, particularly when decreased, may supersede perfusion considerations alone. For example, a decreased blood flow may produce anoxia, which in turn may affect hepatocellular activity and hence the extraction ratio. The extraction ratio may also be altered by a decreased blood flow

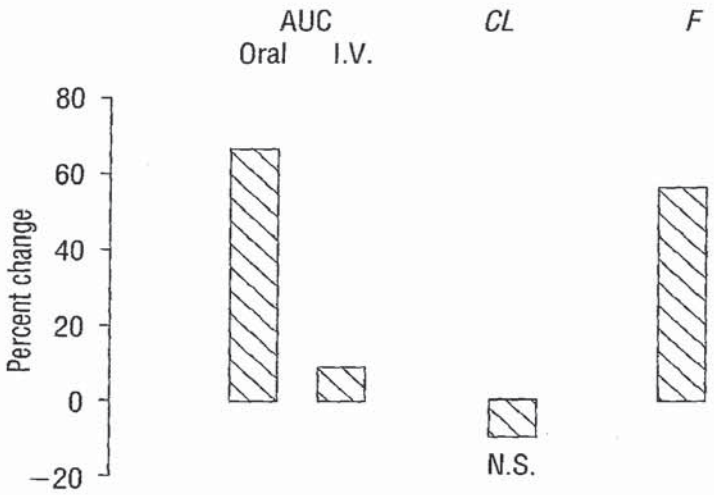

Fig. 12–5. Bioavailability increased, but clearance showed no significant (N.S.) change, when 6 healthy volunteers were given labetolol either as a 200-mg dose orally or as a 0.5-mg/kg dose i.v. before and on the fourth day of cimetidine treatment (400 mg every 6 hr). This conclusion is based on a significant change in *AUC* after oral, but not after i.v. administration. (Adapted from Daneshmend, T.K., and Roberts, C.J.C.: The effects of enzyme induction and enzyme inhibition on labetolol pharmacokinetics. Br. J. Clin. Pharmacol., *18*:393–400, 1984.)

because every blood vessel in the organ may not provide the same exposure of the drug to hepatic parenchymal cells, and the pattern of distribution of blood flow within the eliminating organ may change. This alteration in the degree of shunting or bypassing of the parenchymal cells may occur in certain hepatic diseases and under a variety of conditions.

Good examples of the kinetic consequences of altered blood flow are hard to find. This is not because they are uncommon, but because a number of additional complications always seem to occur concurrently. For example, conditions such as congestive cardiac failure, in which cardiac output is decreased, are often associated with increased third-spacing (build-up of fluid in intestinal spaces and body cavities), diminished hepatic and renal functions; and slowed distribution to the tissues. A decrease in hepatic blood flow, brought about by cirrhosis, chronically leads to portal hypertension and extrahepatic shunting of portal blood. Thus, the kinetic consequences of altered blood flow are subsequently examined alone, with the realization that in therapeutic scenarios the effects of changes in more than one physiologic variable need to be considered.

For this theoretical presentation, consider the two drugs given in Table 12–3. Drug L is eliminated in both the liver and the kidneys; its major property is low extraction in both organs. Drug H has a high hepatic extraction ratio and is almost exclusively eliminated by the liver.

Low Hepatic Extraction Ratio. Figure 12–6 shows the effect of a doubling of hepatic blood flow for the poorly cleared drug, drug L. Because drug L has a low hepatic extraction ratio, altered blood flow has little or no effect on the pharmacokinetics of this drug.

High Hepatic Extraction Ratio. The events following i.v. administration of a drug with a high hepatic extraction ratio, drug H, when hepatic blood flow is increased, are readily apparent. Not so apparent are the likely events that follow when drug H is given orally. Recall that $F \cdot \text{Dose} = CL \cdot AUC$ or $AUC = F \cdot \text{Dose}/CL$. Although the half-life is shortened, clearance and oral bioavailability are increased simultaneously; oral bioavailability is elevated because drug in blood remains in the hepatic sinusoids for a shorter period of time with an increased blood flow, and therefore there is less chance of drug being eliminated. Accordingly, the result may be little or no change in AUC (last graph of Fig. 12–6). The outcome depends on whether or not the increase in bioavailability is exactly matched by that of clearance when blood flow is increased. The memory aids of Eqs. 2 and 3 predict equal effects, in that the ratio of these equations ($CL_b/F_{II} = CL_{int} \cdot fu_b$) is independent of blood flow. Unfortunately, there is a lack of good quantitative information to be specific here.

An example of a change in kinetics with a change in blood flow is given with lidocaine in Fig. 12–7. Lidocaine is a drug with a high hepatic extraction ratio and whose clearance is perfusion rate limited. Here, as expected, the concurrent administration of either β-blocker, propranolol or metoprolol produces a decrease in the clearance of lidocaine. β-Blockers reduce cardiac output and hepatic blood flow. The change in lidocaine clearance following propranolol administration is larger than that expected for the change in hepatic blood flow, suggesting that one or more other mechanisms may also be operating.

Table 12–3. Pharmacokinetic Parameters of Two Hypothetical Drugs

DRUG	BIOAVAILABILITY[a]	VOLUME OF DISTRIBUTION (L)	CLEARANCE[b] (L/hr)	FRACTION EXCRETED UNCHANGED	EXTRACTION RATIO	
					HEPATIC	RENAL
L	0.97	26	6	0.60	0.03	0.05
H	0.05	430	77	0.05	0.95	0.06

[a]Bioavailability is fully accounted for by first-pass metabolism in the liver.
[b]Clearance is based on measurement of drug in blood.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.