# The Effect of Chronic Renal Failure on Hepatic Drug Metabolism and Drug Disposition

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## ABSTRACT

There is abundant evidence that chronic renal failure (CRF) and end-stage renal disease (ESRD) alter drug disposition by affecting protein and tissue binding and reducing systemic clearance of renally cleared drugs. What is not fully appreciated is that CRF can significantly reduce nonrenal clearance and alter the bioavailability of drugs predominantly metabolized by the liver. Animal studies in CRF have shown a major down-regulation (40–85%) of hepatic cytochrome P-450 metabolism involving specific isozymes. Phase II reactions such as acetylation and glucuronidation are also involved, with some isozymes showing induction and others inhibition. Hepatic enzymes exhibiting genetic polymorphisms such as N-acetyl-transferase-2 (NAT-2), which is responsible for the rapid and slow acetylator phenotypes, have been shown to be inhibited by ESRD and reversed by transplantation. There is some evidence pointing to the possibility of inhibitory factors circulating in the serum in ESRD patients which may be dialyzable. This review includes all significant animal and clinical studies using the search terms "chronic renal failure," "cytochrome P-450," and "liver metabolism" over the past 10 years obtained from the National Library of Medicine MEDLINE database, including relevant articles back to 1969.

There is a tacit assumption that the clearance and distribution of drugs that are removed from plasma exclusively by hepatic metabolism are not affected by chronic renal failure (CRF). Therefore no dose adjustments are necessary in hepatically cleared drugs in this population. This is a widespread misconception, primarily due to a lack of information, which is not supported by investigations spanning several decades. The purpose of this review is to outline the different ways in which drug disposition is altered by CRF, cite specific drugs of clinical concern, and discuss proposed mechanisms. Citations were derived from MEDLINE (1990–2001) using the search terms "liver metabolism," "chronic renal failure," and "cytochrome P-450" including other relevant articles dating back to 1969.

## Background Pharmacokinetics

In order to understand the various effects of CRF on drug disposition it may be helpful to review some basic pharmacokinetic concepts [1]. Systemic clearance ($CL_{SYS}$) is equal to the sum of renal ($CL_R$) and nonrenal ($CL_{NR}$) clearances:

$$CL_{SYS} = CL_R + CL_{NR} \qquad (1)$$

Renal clearance is defined as the amount of drug eliminated per unit time in the final urine normalized to plasma concentration:

$$CL_R = UV/P, \qquad (2)$$

where $U$ is the urine concentration, $P$ is the plasma concentration, and $V$ is the urine flow rate.

Renal drug metabolism according to this definition is not a component of $CL_R$, but rather is incorporated into the nonrenal clearance term $CL_{NR}$. The renal cytochrome P-450 activity is 20% of the hepatic cytochrome P-450 activity per gram of tissue and the kidney participates in conjugation reactions as well [2,3]. However, the total renal mass is one-fifth of the hepatic mass and therefore renal cytochrome P-450 may contributes a minor fraction of the total activity. Nevertheless, for drugs which are highly extracted by the kidney and whose metabolism is therefore blood flow limited, the kidney may play a more significant role, since renal blood flow is three- to fivefold greater than hepatic blood flow per gram of tissue [4]. Of course, this renal drug metabolizing capacity deteriorates with the progression of CRF, leading to a reduction in nonrenal clearance independent of any effects on the liver or intestinal metabolism.

Nonrenal clearance and the distribution volume of drugs is altered by CRF via changes in hepatic clearance, plasma protein binding, and tissue binding. CRF has been shown to decrease plasma protein binding of acidic drugs, increasing the free (unbound) fraction ($f_u$), as shown in Table 1 [5–18]. The mechanism is presumably the reduction of the apparent binding affinity to albumin due to conformational changes in albumin or

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competition with unmeasured small molecules and accumulated metabolites that are not entirely removed by dialysis (19,20).

CRF increases plasma levels of α1-acid glycoprotein which is induced in acute and chronic inflammation. The α1-acid glycoprotein binds basic drugs and one would predict increased binding of these drugs in CRF. However, in most cases drug binding is reduced or remains unchanged and is only occasionally increased, as shown in Table 1 (6). The reduced binding of basic drugs to α1-acid glycoprotein may result from mechanisms similar to those that impair the binding of acidic drugs to albumin, such as reduced binding affinity and competing ligands circulating in the plasma of end-stage renal disease (ESRD) patients.

CRF has also been shown to decrease the distribution volume ($V_d$) of drugs such as digoxin, which has its $V_d$ reduced by 50% in ESRD due to reduced tissue binding (2). The opposite effect is observed with phenytoin, which shows a twofold increase in $V_d$ in ESRD due to reduced plasma protein binding (2). Furthermore, CRF reduces hepatic clearance of drugs by mechanisms which will be discussed later.

The determinants of hepatic clearance will be better understood after a further discussion of clearance concepts (1,21). The rate of extraction of a drug across an organ of elimination is described by the blood flow through the organ ($Q$) and the concentrations of the drug at the arterial side (input) ($C_A$) and at the venous side (output) ($C_V$) as shown in the equation 3. Extraction ratio ($E$) is the rate of extraction divided by the rate of presentation (equation 4). Clearance ($CL$) is the rate of extraction normalized to $C_A$ (equation 5). Hepatic clearance ($CL_H$) is equal to hepatic blood flow multiplied by $E_H$ (equation 6).

$$\text{Rate of extraction} = Q(C_A - C_V) \qquad (3)$$

$$E = \text{rate of extraction/rate of presentation}$$
$$= C_A - C_V/C_A \qquad (4)$$

$$CL = \text{rate of extraction}/C_A$$
$$= Q(C_A - C_V)/C_A \qquad (5)$$

**TABLE 1. Drugs with changes in protein binding in CRF**

| Drug type | Change in binding |
| --- | --- |
| Acidic | |
| Desmethyldiazepam | Decreased |
| Phenytoin | Decreased |
| Valproic acid | Decreased |
| Salicylate | Decreased |
| Phenylbutazone | Decreased |
| Furosemide | Decreased |
| Warfarin | Decreased |
| Sulfamethoxazole | Decreased |
| Basic | |
| Disopyramide | Increased |
| Vancomycin | Decreased |
| Morphine | Decreased |
| Oxazepam | Decreased |

Adapted from Refs. 5 and 6.

$$CL_H = QE_H \qquad (6)$$

If a drug has a high hepatic extraction ratio, $E$ approaches one, then the total hepatic clearance ($CL_H$) is rate limited by hepatic blood flow. With a low-extraction drug, $E$ approaches zero, then total hepatic clearance is rate limited by intrinsic (unbound) clearance ($CL_{INT}$) and free fraction ($f_u$) of drug. The relationship between these parameters is expressed in the well-stirred model of total hepatic clearance ($CL_{HTOT}$) (equation 7) (21):

$$CL_{HTOT} = QCL_{INT}f_u/Q + CL_{INT}f_u. \qquad (7)$$

Intrinsic hepatic clearance relates the rate of metabolism at steady state to the free unbound fraction in blood. If the drug is highly extracted, we assume $CL_{INT}f_u \gg Q$, then $CL_{HTOT} = Q$ and total hepatic clearance is blood flow limited and relatively independent of changes in intrinsic hepatic clearance which may be produced by a down-regulation or induction of hepatic cytochrome P-450. If the drug is a low-extraction agent then we assume $Q \gg CL_{INT}f_u$, then $CL_{HTOT} = CL_{INT}f_u$ and would be highly influenced by changes in plasma protein binding and intrinsic hepatic clearance. These various permutations have been aptly simulated using empirically derived models (22). Hepatic blood plasma flow has been shown to be unaffected by CRF (23). However, concomitant diseases such as congestive heart failure and chronic liver disease are frequently associated with ESRD and are known to reduce hepatic blood flow and $CL_{HTOT}$.

For a highly extracted drug, orally administered, with a large first-pass effect (presystemic clearance) and low systemic bioavailability ($F$), the magnitude of the first-pass effect can be estimated by equation 8 (1,21):

$$F = Q_H/Q_H + CL_{INT}f_u. \qquad (8)$$

For highly extracted drugs, $CL_{INT}f_u \gg Q_H$, then $F = Q_H/CL_{INT}f_u$. Therefore changes in intrinsic hepatic clearance and plasma protein binding induced by CRF would be predicted to produce significant changes in systemic bioavailability. For example, a reduction in intrinsic hepatic clearance would reduce first-pass metabolism, causing a sizable increase in bioavailability of a highly extracted drug, leading to a clinically significant increase in steady-state plasma concentration.

In summary, CRF can significantly affect the disposition of both low and high hepatic extraction drugs which are cleared predominantly by the liver (Table 2). Hepatic clearance of low-extraction drugs is limited by intrinsic hepatic clearance and plasma protein binding. A reduction in intrinsic hepatic clearance will lead to reduced systemic clearance and produce an increase in steady-state plasma levels for both free and total drug concentrations of low-extraction drugs. Reduced plasma protein binding leading to increased free fraction ($f_u$) will also produce an elevated total hepatic clearance that leads to a reduction in total steady-state drug concentrations but no change in free concentrations as long as intrinsic hepatic clearance is unchanged. Since free concentrations are presumably the biologically active fraction, then the result may have little clinical impact.

**TABLE 2. Summary of the effects of CRF on pharmacokinetic parameters**

*Low hepatic extraction drugs ($E_H < 0.20$)*
Cytochrome P-450 down-regulation, circulating inhibitors $\rightarrow CL_{INT}\downarrow \rightarrow CL_{TOTHEP}\downarrow C_T\uparrow C_u\uparrow$
  (Acidic drugs) $\rightarrow$ PPB$\downarrow \rightarrow CL_{TOTHEP}\uparrow C_T\downarrow C_u\leftrightarrow$

*High hepatic extraction drugs ($E_H > 0.80$)*
Cytochrome P-450 down-regulation, circulating inhibitors $\rightarrow CL_{INT}\downarrow \rightarrow F\uparrow$
  (Acidic drugs) $\rightarrow$ PPB$\downarrow \rightarrow F\downarrow$

Hepatic extraction, $E_H$; total hepatic clearance, $CL_{TOTHEP}$; total steady-state plasma concentration, $C_T$; free steady-state plasma concentration, $C_u$; intrinsic hepatic clearance, $CL_{INT}$; plasma protein binding, PPB; bioavailability, $F$.

For high-extraction drugs, total hepatic clearance is blood flow limited. Since hepatic blood flow is not altered in renal failure, total systemic clearance should not be affected by changes in intrinsic hepatic clearance or plasma protein binding. However, first-pass metabolism (presystemic clearance) is a function of $CL_{INT}$ and $f_u$, so changes in these parameters will result in significant changes in systemic bioavailability, as much as several fold for high-extraction drugs.

## Animal Studies: Effect of Renal Failure on Cytochrome P-450 Metabolism

### Acute Renal Failure Models

Animal studies spanning several decades have shown reduced hepatic microsomal enzyme activity in experimental models of acute and chronic renal failure. In rats with acute renal failure (ARF) (produced by subtotal nephrectomy), hepatic microsomal protein content (per gram of liver) was reduced (24). Demethylation of aminopyrine and p-nitroanisole, and para-hydroxylation of acetanilide also dropped by 30–50%. There was stimulation of O-demethylation of p-nitroanisole by 125%. Intraperitoneal injections of δ-aminolevulinic acid normalized total microsomal protein cytochrome P-450 content but did not reverse the inhibition of cytochrome P-450 activity. In other rat models of ARF (induced by bilateral ureteral ligation or uranylnitrate injection), a reduction of aminopyrine N-demethylation was seen (25). Total cytochrome P-450 and aniline hydroxylation was reduced as well, but did not reach statistical significance.

An example of how the pharmacokinetics of a highly extracted, extensively metabolized drug can be altered by experimental renal failure in the intact rat is illustrated by the following study using a rat model in which ARF is induced by uranyl nitrate (26). Following injection of ARF rats and controls with intravenous levopropranolol, no differences in the area under the plasma drug concentration versus time curve (AUC) or plasma clearance were seen. Using the same protocol with oral levopropranolol, the ARF rats showed a 2.5-fold increase in systemic bioavailability from 7 to 18%. The same investigators then studied levopropranolol first-pass metabolism in isolated perfused rat liver (27). Liver from normal rats perfused with normal blood yielded a 97.4% extraction ($E_H$) of levopropranolol. Livers from ARF rats perfused with uremic blood yielded a levopropranolol extraction of 90.6%. This resulted in a greater than threefold increase in bioavailability ($F$) (2.6–9.4%) consistent with the data from intact animals and

corresponding to a 50% drop in $CL_{INT}$. When livers from normal rats were cross-perfused with uremic blood, $E_H$ was reduced to 92.7%, not significantly different from the uremic livers perfused with uremic blood. Surprisingly, uremic livers cross-perfused with normal blood showed an $E_H$ of 97.0%, identical to the control normal livers perfused with normal blood. These data suggest that cytochrome P-450 metabolism of propranolol in uremic rats is not down-regulated but that a rapidly acting inhibitory factor exists in uremic serum.

### Chronic Renal Failure Models

A study utilizing a CRF rat model induced by subtotal nephrectomy showed a 24–32% decrease in hepatic N- and O-demethylation activities, whereas S-demethylase, esterase, UDP-glucuronyl transferase, and monoamine oxidase were not altered (28). Alcohol dehydrogenase activity increased by 71% and cytochrome P-450 levels decreased by 26%. CRF also increased hexobarbital sleeping time. In each case alterations correlated with extent of CRF.

Over the past 15 years the cytochrome P-450 gene superfamily has been sequenced and various isozymes and isozyme-specific probe drugs have been identified. In a CRF model in rats using subtotal nephrectomy, the effect of CRF on the activity of various cytochrome P-450 isozymes, in vivo, was investigated using $^{14}$C-labeled caffeine (CYP1A2), aminopyrine (CYP2C11), and erythromycin (CYP3A2) breath tests (29). There was a 35% reduction in CYP2C11 and CYP3A2 activities and no difference in CYP1A2 as measured by their respective breath tests. Total cytochrome P-450 was reduced by 40% and protein expression of CYP2C11, CYP3A1, and CYP3A2 in CRF rats was reduced by 45%, 85%, and 45%, respectively; CYP1A2 did not change. There was also a significant correlation between cytochrome P-450 activity measured by breath tests and protein expression of the various cytochrome P-450 isozymes.

A later study by the same investigators also confirmed these findings (30). Protein expression of CYP2C6, CYP2D, and CYPE1 also remained constant. Northern blot analysis showed a down-regulation in gene expression in CYP2C11, CYP3A1, and CYP3A2 with no change in the expression of the remaining cytochrome P-450 isozymes tested. Phenobarbital and dexamethasone maintained their ability to induce CYP3A1 and CYP3A2 isozymes. Demethylation of erythromycin (CYP3A2) was reduced by CRF, which was reversed by treatment with phenobarbital and dexamethasone.

In a CRF model (45 days of severe uremia in rats caused by subtotal nephrectomy), no induction of

microsomal cytochrome P-450 enzymes occurred (31). However, induction of the phase II reaction, glucuronidation, did occur (77% increase in activity). Total cytochrome P-450 content (in nmol/mg of protein) was reduced by 45%. P-nitroanisole activity was reduced by 40%, aminopyrine by 35%, and acetanilide by 40%. Treatment with the plasticizer di(2-ethylhexyl)phthalate caused a 54% increase in liver wet weight and 65% increase in microsomal protein content, a 23% increase of demethylation of aminopyrine and a threefold reduction in hexobarbital sleeping time in CRF rats but not in sham-operated controls. These results and those of the previous study (30) suggest that known enzyme inducers can partially reverse the effects of CRF on hepatic cytochrome P-450 metabolism and that phase II reactions such as glucuronidation are relatively preserved and in some cases stimulated by CRF.

In summary, various animal models of ARF and CRF have shown reduced activity of hepatic cytochrome P-450 in which certain pathways appear to be affected and others remain intact. Later studies have shown that certain cytochrome P-450 isozymes are down-regulated and that reduced protein expression correlates with reduced cytochrome P-450 activity measured by specific probes, while the expression of other isozymes and their activity remains unchanged. Surprisingly levopropranolol hepatic extraction is inhibited by uremic blood in perfused normal rat liver. Uremic livers showed no impairment in hepatic first pass when perfused with normal blood, suggesting a rapidly acting circulating competitive inhibitor of cytochrome P-450 activity without down-regulation of cytochrome P-450 expression in the uremic liver. This is consistent with the finding that CYP2D6, the isozyme that metabolizes levopropranolol, is not down-regulated in rat CRF models and suggests that two mechanisms may explain the reduced cytochrome P-450 activity: circulating factors and decreased protein expression. Some phase II reactions such as glucuronidation appear to be stimulated in CRF. The mechanisms for these phenomena have not been elucidated.

### Clinical Investigations: Effect of CRF on Drug Disposition

A number of reviews on the effect of CRF on drug disposition exist in the literature (2,4,5,32–34). One of the earliest clinical studies showed a reduction in the nonrenal elimination (acetylation) of sulfisoxazole given intravenously to patients with CRF and questioned the concept of therapeutics prevalent in the 1960s that azotemic patients should receive the usual doses of drugs eliminated by hepatic metabolism (34,35). A later review showed decreased reduction, acetylation, and hydrolysis reactions but preserved sulfation, glucuronidation, and oxidation reactions (34).

Clinical data exist showing significant alterations in nonrenal clearance in CRF for a number of drugs (Table 3) (36–61). The majority of these studies involve ESRD patients; a few included subjects with moderate to severe CRF. These alterations include both substantial

**TABLE 3. Effect of CRF on nonrenal clearance**

| Drug | Change in nonrenal clearance (%) | Metabolism |
|---|---|---|
| Increased | | |
| Phenytoin | 57 | CYP2C9, 2C19 |
| Fosinopril | 70 | NA |
| Bumetanide | 57 | NA |
| Decreased | | |
| Acyclovir | 50 | NA |
| Aztreonam | 33 | NA |
| Cefotaxime | 40 | NA |
| Cilastin | 92 | NA |
| Imipenem | 58 | NA |
| Moxalactam | 63 | NA |
| Captopril | 50 | Sulfoxidation |
| Procainamide | 60 | NAT-2 |
| Nimodipine | 87 | CYP3A4 |
| Verapamil | 54 | CYP3A4 |
| Metoclopramide | 66 | CYP2D6 |
| Desmethyldiazepam | 63 | CYP2C9 |
| Warfarin | 50 | CYP2C9 |

NA, not available.

**TABLE 4. Effect of CRF on bioavailability**

| | |
|---|---|
| Propranolol | Increased |
| Erythromycin | Increased |
| Tacrolimus | Increased |
| Propoxyphene | Increased |

reductions and increases (36,39) in nonrenal clearance ranging from 30 to 90%. In the case of phenytoin, the 50% increase in total hepatic clearance is produced by a two- to threefold increase in free fraction ($f_u = 20$–30%) due to reduced plasma protein binding (normal $f_u = 10$%) (10,36). This results in a reduction in steady-state total phenytoin concentration to 5–10 µg/ml with no change in free concentration (1–2 µg/ml) because intrinsic hepatic clearance is not altered. Increasing the dose of phenytoin to achieve a target concentration of 10–20 µg/ml for total phenytoin may raise free concentrations to toxic levels.

For high-extraction drugs, the effect of CRF is manifest as an increase in bioavailability ($F$), as shown in Table 4 (36,61–64). The plasma AUC of propoxyphene was increased twofold in ESRD (61). For erythromycin, CRF results in a fourfold increase in plasma AUC after an oral dose (62,63). Half-life is unchanged and $V_d$ is increased in renal failure, suggesting that the increase in AUC was due to an increase in $F$ because of reduced hepatic uptake.

In patients with CRF approaching ESRD, oral propranolol showed a bioavailability of 62%, compared with 32% in ESRD patients on hemodialysis and 19% in healthy volunteers (64). This is in agreement with the previous animal data showing an increase in $F$ for propranolol in uremic rats and consistent with the pharmacokinetic principle that the bioavailability of high hepatic extraction drugs is increased with reductions in intrinsic hepatic clearance. The same investigators also found that the bioavailability of propranolol was greater on the day of dialysis (43%) compared to the day after dialysis (34%). These findings are in agreement with the

animal data in isolated perfused livers which suggest that a circulating dialyzable inhibitory factor is present in uremic serum. However, another investigator found no significant difference in apparent oral clearance, total clearance, or bioavailability of propranolol in stable renal failure patients with creatinine clearance of approximately 15 ml/min (65). It is possible that in these patients there is enough residual renal function to prevent the inhibition of hepatic metabolism.

Zidovudine is eliminated primarily by glucuronidation and 25% is excreted unchanged by the kidneys. The plasma AUC was doubled in the CRF group receiving a single 200 mg oral dose, indicating a decrease in intrinsic hepatic clearance, suggesting that hepatic conjugation reactions can be reduced in CRF (66).

Another conjugation reaction, acetylation, is also altered in ESRD. N-acetyltransferase (NAT-2) exhibits genetic polymorphisms, with approximately half of the African American and Caucasian populations exhibiting either the rapid or the slow acetylator phenotype. The effect of ESRD on acetylator phenotype was addressed in the following study (67). First, isoniazid and acetylisoniazid pharmacokinetics were determined after a single 400 mg oral dose of isoniazid and the same protocol repeated after renal transplantation. Based on the half-life of isoniazid and using the criteria of Reidenberg et al. (68), patients were divided into rapid and slow acetylator groups. The pharmacokinetic parameters were compared pre- and post-transplantation within each phenotypic group. There was a 50% reduction in $CL_{NR}$ in CRF patient in the rapid acetylators which was reversed by transplantation and there was a threefold reduction in $CL_{NR}$ in slow acetylators which was also reversed by transplantation. This demonstrated that ESRD affected the NAT-2 phenotype, reducing the activity of both rapid and slow acetylators, and the slow acetylator phenotype was inhibited to a much greater extent.

These data suggest that drugs which are cleared extensively by the liver and exhibit polymorphic metabolism may be at much higher risk of adverse drug reactions in CRF, since the poor metabolizer phenotype may be more susceptible to the inhibitory effects of CRF on metabolism (67). We have preliminary data from our hemodialysis unit to show that ESRD reduces hepatic CYP2C9 activity by 50% as measured by the S/R warfarin ratio as a phenotypic probe (69). (S-warfarin is metabolized exclusively by CYP2C9, while R-warfarin is metabolized by multiple pathways.)

## Conclusion

There is abundant evidence that nonrenal clearance, protein binding, and distribution volume of drugs are altered in CRF increasing the risk of adverse drug reactions. The majority of the data are in patients with ESRD. Even drugs cleared predominantly by the liver are significantly affected, especially those which exhibit genetic polymorphisms (67,69). Caution should be exercised in dosing the drugs in Tables 3 and 4, which show significant reductions in nonrenal clearance and

increased bioavailability. Careful titration from the lowest dose should be attempted.

One mechanism of the reduced nonrenal clearance appears to be down-regulation of protein expression of specific hepatic cytochrome P-450 isozymes. Phase II reactions such as glucuronidation and acetylation are affected, showing inhibition or induction. This appears to be isozyme specific, as well. There is also evidence that, at least in the case of propranolol (CYP2D6), there may be circulating inhibitors in the serum of ESRD patients which may be dialyzable. Otherwise there are scant data available concerning the effect of dialysis on these changes in nonrenal clearance. More pharmacokinetic studies investigating the effect of CRF on nonrenal clearance, bioavailability, and plasma protein binding of extensively metabolized drugs and mechanisms of these phenomena and the effect of dialysis are needed.

## Acknowledgment

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