15

DRUG-PROTEIN BINDING IN LIVER DISEASE AND IN PATIENTS WITH HYPOALBUMINEMIA

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HYPOALBUMINEMIA

When the Boston Collaborative Drug Surveillance Program reported in 1973 an increased incidence of side effects from phenytoin, a highly protein bound drug, in patients with hypoalbuminemia,[3] it was concluded that these findings might be related to decreased plasma protein binding of phenytoin producing an increase in the pharmacologically active free drug concentration. Hypoalbuminemia is, however, associated with a large variety of pathological conditions, a number of which are shown in Table 15.1. It may be generalized that almost any serious chronic illness can be associated with hypoalbuminemia, but most of the conditions listed in Table 15.1 lead to additional organ disturbances which affect drug disposition—e.g., liver cirrhosis or renal insufficiency. The nephrotic syndrome in patients with essentially normal renal function is a suitable model to study the effects of pure hypoalbuminemia on drug binding and pharmacokinetics.[10]

The plasma concentrations of chlorophenoxyisobutyric acid (CPIB), the active metabolite of clofibrate, were determined during steady-state treatment with clofibrate in a group of six patients with nephrotic syndrome.[8] Compared to a control group, CPIB levels were consistently lower in the nephrotic patients both during treatment and after the final clofibrate dose (Figure 15-1). The plasma level decline also appeared steeper in the patient group. Steady-state

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TABLE 15.1
Conditions Associated with Hypoalbuminemia

Old age
Pregnancy
Liver cirrhosis
Renal failure
Nephrotic syndrome
Chronic inflammation
Cancer
Protein losing enteropathy
Sepsis

plasma concentrations of CPIB were 47.9 ± 6.8 μg/ml in the nephrotics and 133.5 ± 12.0 μg/ml in the controls (Figure 15-2). The plasma elimination half-life was reduced from 21.3 ± 1.4 to 12.3 ± 1.2 hours in the patient group. The plasma protein binding of CPIB was decreased in the nephrotic patients leading to an increase in unbound CPIB from 3.6 ± 1.0 percent to 11.2 ± 3.9 percent of the total concentration (Figure 15-2).

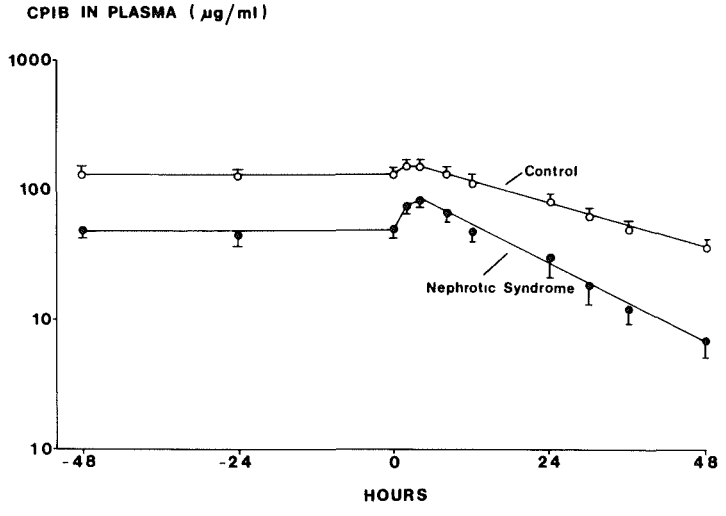

FIGURE 15-1
Mean plasma concentrations of chlorophenoxyisobutyric acid (CPIB) during steady-state and after the final dose of clofibrate 1 g bid in control subjects, and in patients with the nephrotic syndrome.

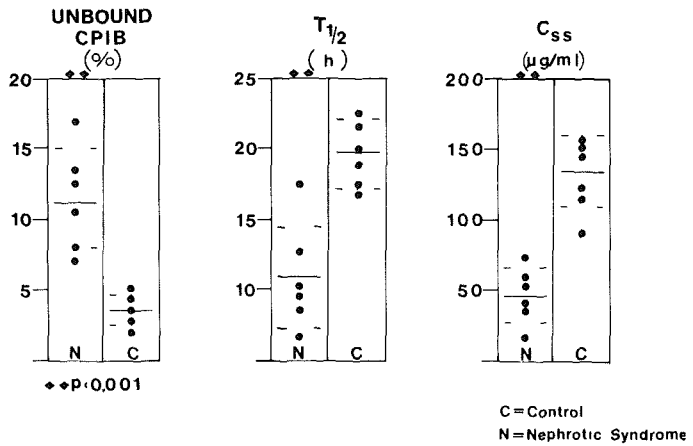

FIGURE 15-2
Unbound CPIB fraction, plasma elimination half-life ($T_{\frac{1}{2}}$), and steady-state plasma concentration (Css) of CPIB in nephrotics and in controls.
Source: Gugler et al. 1975a. (Reprinted with permission.)

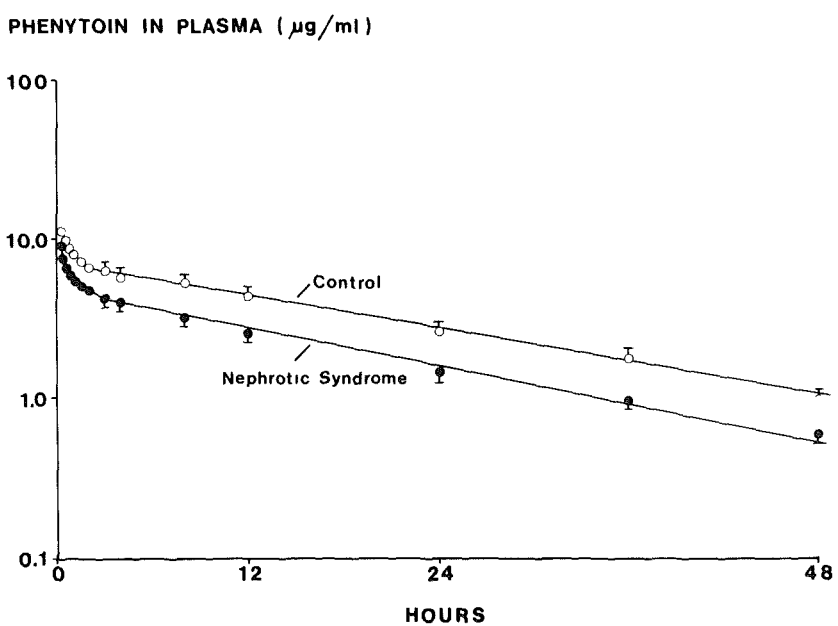

FIGURE 15-3
Mean plasma phenytoin concentrations following single intravenous administration of 300 mg to patients with nephrotic syndrome and to control subjects.

Following a single 300 mg intravenous dose of phenytoin, plasma concentrations over 48 hours were consistently lower in the nephrotic patients compared to a control group (Figure 15-3), but the plasma level decline appeared similar in both groups. The individual pharmacokinetic parameters of phenytoin were also determined during steady-state treatment.[8] Steady-state plasma concentrations were reduced from 6.9 ± 0.5 μg/ml in the control group to 2.9 ± 0.2 μg/ml in the nephrotic group (Figure 15-4). The unbound phenytoin fraction increased from 10.1 ± 0.4 to 20.0 ± 1.3 percent in the nephrotics. Total systemic plasma clearance of phenytoin was significantly increased from 22 ± 6 in the controls to 48 ± 19 ml/kg×h in the nephrotics, but the change in elimination half-life (14.6 ± 1.8 nephrosis; 18.0 ± 1.1 control) was not significant. The volume of distribution (Vd_β) was increased in the nephrosis group from 0.29 ± 0.08 to 0.59 ± 0.13 l/kg.

A close correlation was observed between the individual albumin concentration in plasma and the percent unbound fraction of phenytoin.[9] From this relationship, the degree of phenytoin binding to plasma protein can be predicted from the albumin concentration.

When the total plasma clearance of phenytoin in nephrotic patients and in control subjects was plotted against the fraction of unbound phenytoin (Figure 15-5), a linear relationship was observed ($p < 0.01$) with the regression line intersecting close to the origin.[10] Levy and Yacobi[15] have described a pharmacokinetic model from

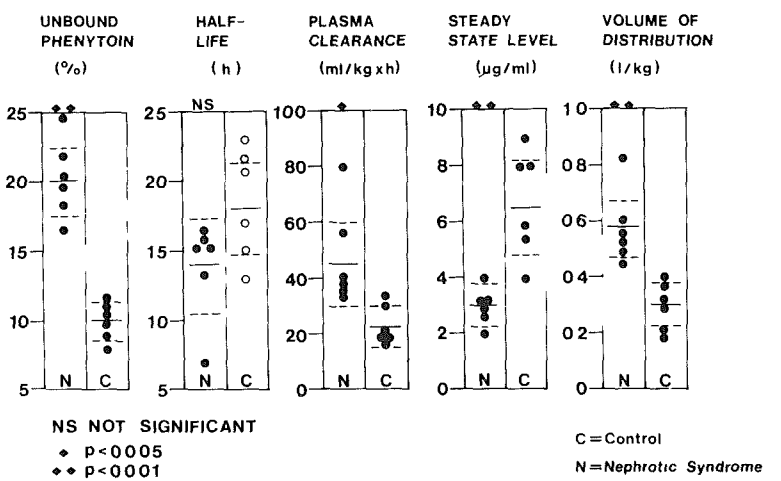

FIGURE 15-4
Phenytoin binding and kinetics in nephrotic syndrome.
Source: Gugler et al. 1975a. (Reprinted with permission.)

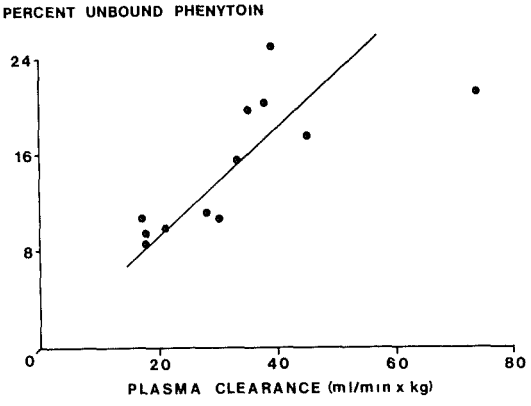

FIGURE 15-5
Unbound phenytoin fraction and total plasma clearance of phenytoin in control subjects and in patients with nephrotic syndrome.

which such a relationship would only be valid if: (1) binding of the drug is constant over the concentration range observed, (2) elimination is only from the central compartment, (3) the concentration of the unbound drug is the driving force over the rate-limiting step of elimination, (4) elimination is not rate-limited by the rate of organ perfusion, and (5) elimination follows first-order kinetics. From these assumptions only (5) is not fulfilled in the case of phenytoin, but the non-linearity of the elimination process may not be relevant in the lower concentration range following single-dose administration.

The changes in drug disposition produced by hypoalbuminemia present a complex picture. The plasma protein binding of normally highly bound acidic drugs is reduced in relation to the degree of albumin concentration. Decreased protein binding is followed by (1) an increase in the distribution volume of the drug, and (2) an acceleration of drug elimination. These compensatory mechanisms result in a decrease in the total plasma concentration of the drugs concerned. Consequently, although the percentage of unbound drug is increased in hypoalbuminemia, the unbound drug concentration may remain unchanged.

LIVER CIRRHOSIS

Acidic Drugs

In patients with liver cirrhosis, albumin synthesis is diminished as a consequence of impaired organ function. As in other conditions

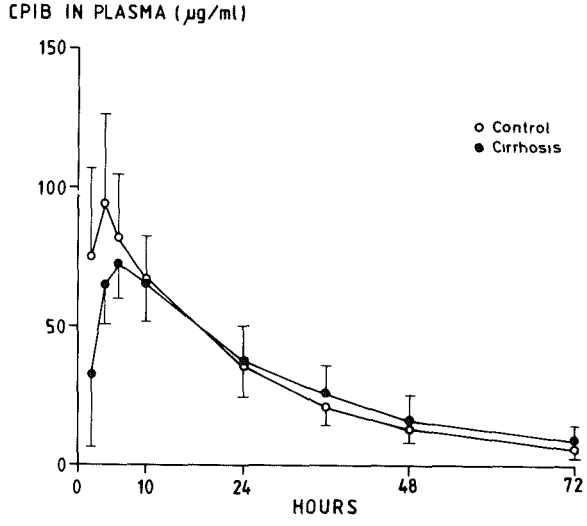

FIGURE 15-6
Mean plasma concentrations of CPIB in patients with liver cirrhosis and in controls following single oral dose of 1 g of clofibrate.

of hypoalbuminemia, one should expect decreased plasma protein binding of acidic drugs and an increased drug elimination due to a greater unbound drug fraction.

Studies with clofibrate in patients with liver cirrhosis[11] have shown, however, that the plasma concentration curves of CPIB following a single oral dose of 1 g of the parent drug were similar to

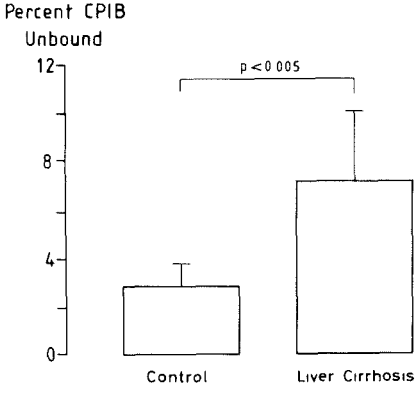

FIGURE 15-7
Unbound CPIB fraction in cirrhotics and in controls.

those of a control group over 72 hours after dosing (Figure 15-6). Only during the initial eight hours were the mean CPIB concentrations lower in the cirrhotic patients, but the difference was not significant due to a large intersubject variation. It should be assumed, based upon these results, that the pharmacokinetics of clofibrate are unchanged in liver cirrhosis.

Determination of plasma protein binding of CPIB revealed that the unbound drug fraction was 7.2 ± 2.9 percent in the patients with liver cirrhosis compared to 3.8 ± 0.9 percent in the control group (Figure 15-7). Therefore, despite identical total plasma concentration of CPIB, the free and presumably pharmacologically active concentration of this drug is increased two-fold, indicative of a parallel increase in drug effect. There appeared to be an inverse correlation between serum albumin concentration and percentage of unbound CPIB, but with the small number of patients studied this was not significant.

The major pharmacokinetic parameters of clofibrate in liver cirrhosis are shown in Figure 15-8. Despite the significant decrease in plasma protein binding of CPIB, the total systemic plasma clearance was unchanged. As is apparent from the mean plasma level-time course of CPIB (Figure 15-6), the plasma elimination half-life was also unaffected. The clearance of the unbound CPIB as calculated from the total plasma clearance, corrected for the percentage of the unbound fraction, was reduced from 243 ± 36 ml/min in the control group to 115 ± 36 ml/min in the patients with liver cirrhosis ($p < 0.05$).

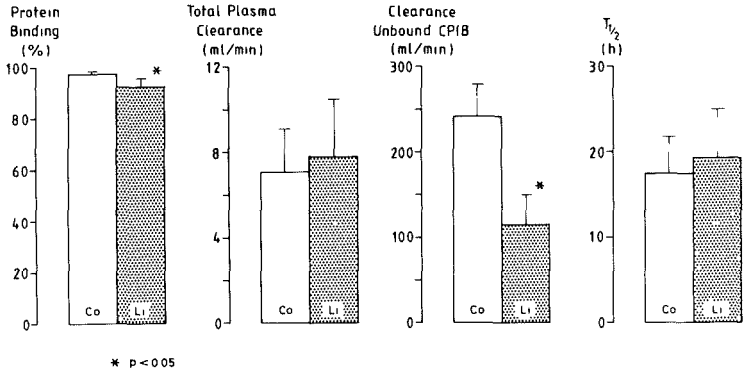

FIGURE 15-8
Drug binding and kinetics of CPIB in liver cirrhosis. $T_{\frac{1}{2}}$ = plasma elimination half-life.

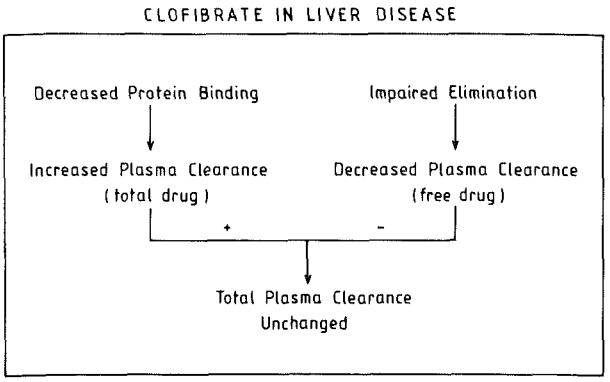

FIGURE 15-9
Scheme of the effect of two counteracting processes on the disposition of clofibrate in liver cirrhosis.

The scheme shown in Figure 15-9 describes the two principal factors which may affect the disposition of highly protein bound acidic drugs in patients with liver cirrhosis. Decreased protein binding leads to an increased plasma clearance of total drug. On the other hand, the impaired elimination capacity of the liver may result in a decrease in unbound drug clearance. The two mechanisms are counteractive and the net effect may be an unchanged total drug plasma clearance, as is the case with clofibrate. Nevertheless, the increased free drug fraction may require a dose reduction in liver cirrhosis which in fact could be overlooked if only the total plasma concentration is considered.

Basic Drugs

It is well recognized that basic drugs differ from acidic drugs in their behavior in blood under the various physiological and pathological conditions.[19,22] While acidic drugs bind primarily to albumin, basic drugs also bind to other protein fractions in plasma.

The plasma protein binding of a large number of basic drugs has been found to be unchanged in liver cirrhosis (Table 15.2), and even the interpatient variation in binding was usually not greater in diseased patients. For several other basic drugs, the binding is significantly reduced in cirrhosis (Table 15.3). It is of interest that the binding of two of the drugs reported (propranolol, triamterene) in the lists is either reduced or unchanged, depending upon the study cited.

TABLE 15.2
Basic Drugs in Liver Cirrhosis: Binding Unchanged

Drug	Control (percent)	Cirrhosis (percent)	Reference Number
Aprinidine	94.6 ± 0.3	90.8 ± 1.6	24
Chlorpromazine	97.9	98.5	21
Clindamycin	79.0 ± 10.6	97.2 ± 7.7	2
Lorcainide	83.3 ± 2.9	80.5 ± 5.7	14
Oxazepam	89.3	87.6	23
Pethidine	64.3 ± 13.5	64.9 ± 5.8	13
Propranolol	84.6-91.7	82.3-92.1	21
Triamterene	56.0 ± 2.0	62.0 ± 3.0	26
d-Tubocurarine	44.4 ± 7.7	39.9 ± 3.1	7
Verapamil	91.0	92.0	6

TABLE 15.3
Basic Drugs in Liver Cirrhosis: Decreased Binding

Drug		Control (percent)	Cirrhosis (percent)	Significance	Reference Number
Dapsone		81.5	58.9	?	1
Diazepam		98.5	92.8	$p < 0.01$	25
Morphine		35.1	25.0	?	17
Nitrazepam		87.0 ± 1.8	81.1 ± 4.3	$p < 0.05$	12
Propranolol		87.8 ± 5.2	82.3 ± 5.7	$p < 0.05$	4
Quinidine	a)	89.0	81.0	?	18
	b)	85.9	59.5	$p < 0.001$	1
Theo-	a)	52.6 ± 3.8	32.3	?	20
phylline	b)	65.0 ± 6.0	29.0 ± 16.0	$p < 0.001$	16
Triamterene		80.7	59-78	$p < 0.01$	1

TABLE 15 4
Alpha-1-Acid Glycoprotein Concentrations in Liver Cirrhosis (mg/dl)

	Control	Cirrhosis
Mean ± standard deviation	84.7 ± 5.7	102.0 ± 23.1
Range	66-108	30-252

Source:
Teirlynek, Belpaire, and Andreasen 1982.

These differences in binding are most likely related to differences in the α_1-acid glycoprotein concentrations between individual patients. Alpha-1-acid glycoprotein, which is the major binding protein for basic drugs, is elevated above normal levels in a number of conditions characterized by physiological stress—i.e., myocardial infarction, renal transplantation—but also ulcerative colitis and Crohn's disease.[22] The mean values of α_1-acid glycoprotein in patients with liver cirrhosis are usually within the normal range, although there is considerable variation with some levels well below and other levels above normal.[5] This variation is also well documented from the work of Teirlynck and coworkers shown in Table 15.4.[24]

The relationship between liver cirrhosis and α_1-acid glycoprotein has never been carefully studied. Thus, in most of the reports, the levels of this protein fraction have been determined in patients poorly characterized both for the activity of their liver disease and for the degree of impairment of their liver function. Theoretically, it may be speculated that α_1-glycoprotein levels are normal or above normal in patients with chronic active hepatitis and well-preserved organ function, while in decompensated liver cirrhosis with reduced protein synthesizing capacity, the levels may be low.

In summary, the effect of liver cirrhosis on the plasma protein binding of drugs is different for acidic and basic compounds. The binding of acidic drugs is often reduced when serum albumin concentration is low. The binding of basic drugs in liver cirrhosis is normal or reduced depending on the serum α_1-acid glycoprotein concentration.

SUMMARY

In hypoalbuminemia, as in nephrotic syndrome, plasma protein binding of acidic drugs is reduced. Decreased binding is related to

a decrease in the plasma albumin concentration. Increased unbound drug fraction is associated with increased distribution volume and accelerated elimination of the drug. Unbound drug concentration remains unchanged in pure hypoalbuminemia.

In severe liver cirrhosis, hypoalbuminemia is associated with reduced binding of acidic drugs. Binding of basic drugs is normal or reduced, depending on the concentration of α_1-acid glycoprotein. The increased clearance due to reduced binding and the decreased hepatic clearance due to liver cirrhosis may result in an apparently unchanged total plasma clearance.

NOTES

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