REVIEW PAPERS

Pharmacokinetics and metabolism of furosemide in man

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SUMMARY

The furosemide pharmacokinetics in healthy volunteers and in patients with renal insufficiency and hepatic cirrhosis is presented. On the average, 70% of the oral furosemide dose is absorbed. The drug is 97.6% bound to plasma albumins. The unbound fraction of the drug rapidly increases with albumin concentration below 2 gm per 100 ml. The half-life of furosemide ranges from 0.33 to 1.17 hours in healthy subjects, and from 4.9 to 9.7 hours in patients with advanced renal failure. In uremic patients with liver cirrhosis the elimination half-life is prolonged to more than 10 hours. Non renal clearance of furosemide is not affected by uremia; in uremic patients without liver disease about 60 to 98% of intravenously administered dose of furosemide is excreted with bile within 24 hours. Only about 10% of the drug is eliminated from the body during hemodialysis. The diuretic effect of furosemide is closely related to creatinine clearance: no effect in anuric cases, moderate effect if creatinine clearance is lower than 10 ml/min, and marked effect if creatinine clearance is higher than 10 ml/min. 4-chloro-5-sulfamoylanthranilic acid is the only furosemide metabolite known so far. This metabolite is 1/4 as potent diuretic as the parent substance.

Key-words: Furosemide, diuretic, pharmacokinetics, metabolism man.

Recently many papers have been published dealing with furosemide (1, 2, 3, 8, 10, 11, 14, 16, 19, 20, 26, 32). The present paper has been intended to review more recent data on pharmacokinetics and metabolism of furosemide.

Furosemide (Lasix, 4-chloro-N-(2-furyl-methyl)-5-sulfamoylanthranilic acid) is at present one of the most potent and least toxic diuretics. This is an organic acid of 331 molecular weight, and pKa 3.6-3.9 (23). The physicochemical properties of furosemide result in its rapid absorption from the stomach and excretion with bile. The drug molecule is instable. It readily degrades when exposed to light and even weak acidic solutions.

Most pharmacokinetic data have been obtained using preparations labelled with radioactive sulfur (7, 16, 32, 33) and carbon (20, 22, 26, 27, 28). The drug’s concentration in biologic fluids can also be measured using Bratton and Marshall diazotization method. The drug can be also determined by means of fluorimetric method proposed by Hajdu and Haußler (13) and subsequently modified by Kelly et al. (16).

Absorption

I. Oral administration

A. Healthy persons. — Calesnick et al. (7) found that in two healthy volunteers given 35S-furosemide at the dosage of 50 mg the maximum plasma radioactivity levels were observed after 60 minutes. Kelly et al. (16) observed no differences in drug absorption whether administered in the form of tablets or solution. Detectable serum furosemide levels were noted as early as 10 minutes after administration of the drug in a fasting patient. Peak concentration of the drug (mean concentration 2.2 μg/ml) was observed at 60 to 70 minutes. Administration of the drug after a meal resulted in delayed occurrence of the drug in blood and lower mean furosemide concentration amounting to about 1 μg/ml. After 4 hours the plasma furosemide concentration was slightly lower than the concentrations observed after drug administration...
in the fasting patient. The drug’s absorption in both these observations amounted up to 60 % of administered dose. The Rupp’s (32) investigations also have shown that furosemide was absorbed at the rate of 68 % after being administered at the dosage of 40 mg.

B. Patients with renal insufficiency. — The study performed by Huang et al. (14) in patients with advanced renal failure (mean serum creatinine concentration of 16.2 mg %) have shown the 1 g dose of furosemide is absorbed at an average of 76 %. Maximum plasma drug levels were observed after 4.4 hours following administration (scatter 2 to 9 hours).

II. INTRAMUSCULAR ROUTE OF DRUG ADMINISTRATION

After injection of 4 mg 35S-furosemide in healthy volunteers the peak concentration of radioactivity in plasma was observed at 30 minutes after drug administration (7).

Distribution

A. Drug binding to plasma proteins. — In plasma, the drug appears both in protein bound and free form. The drug was found to bind with albumin only in healthy individuals (2,26). Data on this subject are summarized in table I. No significant changes in the binding upon increasing the drug concentrations up to 36 μg/ml were observed. More than 130-fold increase in furosemide concentration, up to 245 μg/ml, resulted only in doubling of the unbound fraction of the drug. Furosemide is displaced from albumin binding by tolbutamide, sulfisoxazole, acetylsalicylic acid, diazoxide, acetazolamide and phenylbutazone that are known displacers. The drug displaces bilirubin from albumin (30).

The binding of furosemide is decreased in children with nephrotic syndrome. With serum albumin concentration below 2 gm per 100 ml the unbound fraction of the drug was found to rapidly increase (26). Decreased binding of the drug to plasma proteins was also found in the patients with renal and heart failure (2, 3, 19).

B. Binding of the drug to hepatic proteins. — The in vitro investigations have shown that the drug is covalently bound to hepatic microsomal proteins (20, 22). With the involvement of cytochrome P-450 oxydase, the metabolite responsible for hepatic necrosis is produced. In in vivo studies the covalent binding of furosemide metabolite was correlated with the extent of hepatic necrosis and preceded both necrosis and biochemical changes in this organ.

C. Kinetics of the drug in blood. — After intravenous administration the plasma drug concentration decline curve follows different patterns-monoeponential curve (8, 16, 19), biexponential curve (7, 14, 16) or triexponential curve (32). This seems considerably dependent on the time of observation of plasma drug concentration decrease and on the sensitivity of the drug determination method used. Some pharmaco-kinetic data are shown in table II. The data contained in this table can be supplemented by the study of Huand et al. (14), who observed two uremic patients with coexisting hepatic cirrhosis. In these patients the half-life periods of the drug were markedly increased (14.2 and 20 hours, respectively).

D. Distribution of the drug in the body. — According to literature data furosemide is not widely distributed in the organism (8, 14, 16). Its distribution is limited to the intravascular, and, possibly extravascular space. That seems unsurprising as 97 % of administered dose is bound to plasma proteins. However, exact analysis of the distribution volumes of the drug indicates that the same values calculated for unbound fraction of the drug being pharmacologically active and undergoing exchange with the tissues by, for example, Cutler et al. (8), exceed the body weight of healthy persons by a factor of 5, and that of the patients with renal insufficiency by a factor of 7. Similar results can be obtained based on the data from some other papers (14, 16). This method of calculation is justified (6). Quinacrine, whose distribution volume exceeds the body weight by a factor of 1,000 is the best example. Of course, this value does not specify any morphological space but indicates that this drug is considerably concentrated in spaces different from plasma water. In fact, in the example given, the total amount of quinacrine in liver exceeds 1,000-fold the total drug amount in the plasma. The studies on the

### Table I

<table>
<thead>
<tr>
<th>Percent bound</th>
<th>Authors, method of investigation</th>
</tr>
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<tbody>
<tr>
<td>95 ± 2</td>
<td>Forrey et al. (11) ultrafiltration</td>
</tr>
<tr>
<td>96.4 ± 1.4</td>
<td>Andreasen and Mikkelsen (2), ultrafiltration</td>
</tr>
<tr>
<td>97.6 ± 0.17</td>
<td>Prandota and Pruitt (26) equilibrium dialysis</td>
</tr>
</tbody>
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*a Mean ± SD*