Diuretic effect and disposition of furosemide in cystic fibrosis

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Summary. The pharmacodynamics and kinetics of single oral and intravenous doses of furosemide were studied in 9 patients (mean age 18.5 y) with cystic fibrosis.

The diuretic effect of furosemide lasted for 6 h after oral administration and 2 h following intravenous injection of the drug.

The patients with cystic fibrosis had a more pronounced diuretic response both to the oral and intravenous treatments than that reported in normals. Furosemide caused a marked decrease in urine pH for 5 h following the oral dose and between the 2nd and 3rd h after i.v. injection. The baseline nocturnal urine flow rate in 7 of the 9 patients given furosemide orally was increased by 30.6% compared to that reported in healthy subjects.

The bioavailability of furosemide, its mean absorption rate and the mean plasma and urinary elimination half-lives both of the oral and the intravenous drug were similar to those reported in normal subjects. The patients with cystic fibrosis showed, however, about double normal mean total clearance after both the oral and i.v. treatments, and its renal clearance was almost half the plasma clearance. Nonrenal clearance was markedly increased in the patients, which agreed with a considerable decrease in the renal excretion of the drug. The mean apparent volume of distribution was also markedly increased compared to data in the literature. Oral furosemide resulted in a moderate increase in haematocrit and haemoglobin levels in 7 of 9 patients with cystic fibrosis and marked hypokalemia developed in 6 of the 9 patients 6 h after dosing. Pulmonary function tests performed at that time were changed in an inconsistent manner. The sweat test was significantly perturbed in those subjects, although the concentration of chloride in sweat did not fall below 60 mEq/l in any of the sweat samples tested.

Key words: Furosemide; cystic fibrosis; pharmacokinetics; diuretic effect; baseline urine flow

Cor pulmonale frequently occurs in the later stages of cystic fibrosis, in which it has a chronic course and may even exist without heart failure [36]. Rosenthal et al. [47] have shown that hypervolaemia occurs in cystic fibrosis with moderately severe pulmonary involvement. Diuretic therapy is indicated in the treatment of cor pulmonale with heart failure [30, 36]. According to Moss [36], the diuretics of choice in patients with cystic fibrosis are furosemide and ethacrynic acid. In one study [3], furosemide did not affect the serum electrolyte concentration 30 min after intravenous administration of 1 mg·kg⁻¹ simultaneously with amiloride to children with cystic fibrosis. Whitman et al. [59] showed a beneficial effect of moderate acute diuresis of after intravenous administration of 1–3 mg·kg⁻¹ ethacrynic acid to patients with cor pulmonale secondary to cystic fibrosis. The major effect noted was a significant reduction in systemic venous pressure. Recently, Moss [36] suggested that the prophylactic use of diuretics might be helpful in patients with cystic fibrosis in the management of cor pulmonale without heart failure, when the patient's progress was not satisfactory and there was an unexpected gain in weight.

There are reports of altered pharmacological responses to drugs in cystic fibrosis [20, 27, 42, 43]. The objective of the present study was to evaluate the kinetics and corresponding pharmacodynamics and safety of furosemide in cystic fibrosis.

Materials and methods

Patients

Nine patients with cystic fibrosis, ranging in age from 8 to 24.5 y, who required diuretic therapy, were enrolled in the study (Table 1). The diagnosis was based on an appropriate family and clinical history, abnormal sweat test and the presence of pancreatic insufficiency and chronic pulmonary disease. All patients had normal haematocrit, serum albumin, electrolytes, creatinine, BUN and blood glucose concentrations. Three patients had increased SGOT activity, range 54 to 86 U·l⁻¹ (normal 8 to 33 U·l⁻¹). Patient 4 had a porto-caval...
were assayed within 3 days. Fresh urine was measured with an electronic pH-meter and an above. The volume of each urine sample was measured. The pH of possible 6-8, 8-12, and 12-24 h after oral administration. After the administration of furosemide, at hourly intervals for 6 h, and then, if until assayed. Urine was collected by spontaneous voiding before the early diuretic phase and then at hourly intervals, as described early. The values of CLp, CLm, CLr, and Vz were expressed as percentages of the dose. TheCLr of furosemide was calculated from the relationship: 

\[ CL_r = \frac{A_ne}{C_u AUC (t_0 - t)} \]

where CLr is the clearance, Ane is the amount of furosemide excreted in urine from time zero to infinity, and AUC(t0 - t) is the area under the curve of plasma concentration-time curve.

\[ V_z = \frac{dose \times f}{AUC (0 - t)} \]

where Vz is the volume of distribution, dose is the oral dose, and AUC(0 - t) is the area under the plasma concentration-time curve from time zero to infinity.

\[ % f = \left( \frac{AUC_{oral}}{AUC_{i.v.}} \right) \times 100 \]

where % f is the bioavailability of oral furosemide, AUCoral is the area under the curve of plasma concentration-time curve for oral administration, and AUCi.v. is the area under the curve of plasma concentration-time curve for intravenous administration.

\[ CL_t = \frac{Ae (t_0 - t_00)}{AUC (t_0 - t_00)} \]

where CLt is the total clearance, Ae is the amount of furosemide excreted in urine from time zero to infinity, and AUC(t0 - t00) is the area under the curve of plasma concentration-time curve from time zero to a specified time interval.

\[ % f = \left( \frac{AUC_{oral}}{AUC_{i.v.}} \right) \times 100 \]

where % f is the bioavailability of oral furosemide, AUCoral is the area under the curve of plasma concentration-time curve for oral administration, and AUCi.v. is the area under the curve of plasma concentration-time curve for intravenous administration.

\[ CL_r = \frac{A_ne}{C_u AUC (t_0 - t)} \]

where CLr is the renal clearance, Ane is the amount of furosemide excreted in urine from time zero to infinity, and AUC(t0 - t) is the area under the curve of plasma concentration-time curve from time zero to a specified time interval.

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