Sulphamethoxazole/Trimethoprim: Pharmacokinetic Studies in Patients with Chronic Renal Failure

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Summary. The pharmacokinetics of sulphamethoxazole (SMZ) and trimethoprim (TMP) have been investigated in four healthy volunteers, 15 patients with stable chronic renal failure and 3 patients on regular dialysis. The dosage schedule was 400 mg of SMZ and 80 mg of TMP orally every 12 h. The plasma concentrations and urinary excretion have been analysed in terms of a one compartment open model, allowing for elimination by renal excretion and metabolic processes. — At equilibrium the plasma concentrations of unchanged sulphonamide showed no significant correlation with the degree of renal impairment. The accumulation of TMP increased slightly without affecting the concentration ratio of both agents in plasma. In contrast, increasing accumulation of metabolized SMZ was demonstrated in the presence of renal insufficiency. Indirect evidence indicates that rising metabolite levels under these circumstances may lead to a displacement of unchanged sulphonamide from protein binding sites. — The cumulative urinary excretion amounted to 82.4% of the dose of sulphonamide administered, which probably corresponds to the fraction of the compound absorbed. The urinary concentration of biologically active SMZ was slightly below the plasma level, especially in advanced renal failure, but it remained above the minimum inhibitory concentrations reported in the literature. The concentration of TMP in urine was considerably higher than in plasma, it decreased with loss of renal function as did active SMZ.

Key words: Sulphamethoxazole, trimethoprim, pharmacokinetics, uraemia, sulphonamides.

The combination of sulphamethoxazole (SMZ) and trimethoprim (TMP) has been in use as a chemotherapeutic agent for about two years. The synergistic effect on folate metabolism in bacteria made it possible to reduce the dose of both compounds, thus decreasing the incidence of side effects. Combined therapy might also convert the bacteriostatic activity of the separate compounds to a bactericidal effect thus delaying the development of resistance [21]. Of the sulphonamides available, sulphamethoxazole was chosen for combination with trimethoprim because of similarity of their biological half-lives. Standard preparations (Bactrim®, Eusaprim®) with a fixed ratio of the two drugs are available for oral administration.

Sulphamethoxazole/trimethoprim has found extensive application in the treatment of urinary tract infections, especially for the long-term therapy of recurrent bacteriuria. Inevitably, patients with widely different degree of kidney function will receive this combination. It has repeatedly been shown that there is a tendency for sulphonamides to accumulate in the body when renal function is impaired [4, 9, 12, 16]; this has been confirmed for sulphamethoxazole [20, 25]. From a study of the closely related sulfisoxazole it was concluded that both renal excretion and the metabolism of sulphonamides may be slowed in uraemia [22].

Most of these reports have been based on analytical methods which did not permit unequivocal determination of the chemotherapeutically active substance, because the so-called “free” sulphonamide comprises the unchanged compound as well as its glucuronides. The kinetic behaviour of trimethoprim in renal insufficiency has not been fully documented [25, 27].

The purpose of the present study therefore, was to reinvestigate the effect of varying impairment of renal function on the pharmacokinetic characteristics of SMZ and TMP, after both simultaneous and repeated administration in conformity with the customary treatment schedules [6].

Protocol

Healthy volunteers (n = 4) and patients with stable chronic renal insufficiency (n = 15) received 1 tablet of Bactrim® (400 mg SMZ and 80 mg TMP) as a test dose on the first day of the trial. The resulting plasma concentrations were measured 48 h later in order to get preliminary estimates of the extent of drug accumulation. On day 2—9 the maintenance dose of 1 tablet every 12 h was administered, as suggested for long-term therapy. The objective of the study was explained to the patients, all of whom gave their informed consent to the study.

Blood samples were taken daily at the end of a dosage interval, i.e., immediately preceding the next oral dose. Additional samples were drawn on days 1 and 9—11 as shown in Fig. 1. Urine was collected throughout the trial; the duration of the collection periods being the same as the time interval between

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consecutive blood samples. Urinary pH was measured with a glass-electrode after each micturition. Specimens of plasma and urine were frozen and kept at −20°C for chemical analysis.

Patients with terminal renal failure (n = 3), undergoing regular dialysis treatment, were investigated in the same way. In these cases the administration of the drugs was continued for 13 days. To obtain additional information about drug removal by haemodialysis, medication was interrupted four hours prior to treatment by an artificial kidney on days 4, 7 and 11, and was resumed after almost 13 h of dialysis (modified KIIL-dialyzer, 1 m² membrane surface).

All other drugs were stopped at least 3 days before the trial with the exception of digitalis glycosides. Bicarbonate supplements were restricted to patients with severe metabolic acidosis (standard-bicarbonate below 18 meq/l). The intended fluid intake was approximately 2000 ml/day, except for dialysis patients.

Details of each patient and the results of renal function tests are given in Table 1. Inulin-PAH-clearances were determined several days prior to the trial period. Subsequently endogenous creatinine clearances were performed each day (the figures given are average values of ten 24 h-periods per patient). The impairment of renal function was caused by chronic-interstitial nephropathies, except for one patient with chronic glomerulonephritis (D. E.). There was no sign of overt overhydration in any of the patients.

**Laboratory procedures**

Blood and urine samples were examined by

a) absorption-spectrophotometry for total sulphamethoxazole (SMZ) and for the non-acetylated, non-glucuronized sulphonamide fraction (SMZa), representing the chemotherapeutically active compound [24];

b) fluoro-spectrophotometry for non-metabolized trimethoprim [26], giving results in good agreement with the microbiological assay [21].

The influence of protein-binding on antibacterial activity was neglected. Creatinine was determined by a nonspecific autoanalyzer method; insulin by the anthrone method. Blood examinations were performed three times during the trial; urinary sediments were examined on alternate days.

**Pharmacokinetic and statistical analysis**

A one compartment open model with first order input and elimination of active drug by renal excretion and metabolic inactivation seemed adequate to describe the time course of the plasma concentrations of SMZ and TMP [8, 18, 33].

\[
\begin{align*}
\text{Dose absorbed} & \quad \frac{k}{(FD)} \quad \text{Drug in distribution} \quad [C \cdot V] = \frac{k}{(M - U)} \\
\text{Drug in urine} & \quad \frac{U}{(M - U)} \\
\text{Symbols:} & \\
D & = \text{oral dose} \\
FD & = \text{dose absorbed} \\
f & = \text{fraction of dose absorbed which is excreted unchanged} \\
K & = \text{first order rate constant for the sum of all elimination processes with the components } k_r, k_{ar} \\
O & = \text{plasma concentration} \\
V & = \text{apparent volume of distribution defined by this particular model} \\
k_r & = \text{rate constant for first order input} \\
k_{ar} & = \text{first order rate constant for the sum of all elimination processes with the components } k_r, k_{ar} \\
C & = \frac{(FD)}{V} \\
\nu & = \text{time since administration of last dose} \\
\tau & = \text{dosage interval} \\
\end{align*}
\]

Parameter estimates were obtained by a curve fitting procedure using a digital computer programme according to the principle of the least sum of squares (without application of weighting factors). Mathematically this analysis was based on a repetitive Bateman function [8]; this implies that the rate constants are independent of time and dose:

\[
C = \left(\frac{FD}{V}\right) \left(\frac{k}{k - K}\right) \left[\frac{1 - e^{-K\tau}}{1 - e^{-k\tau}} - \frac{1 - e^{-K\nu}}{1 - e^{-k\nu}}\right]
\]

\[
n = \text{number of single doses} \\
\tau = \text{dosage interval} \\
\nu = \text{time since administration of last dose}.
\]

The parameters obtained were the fictive initial concentration in plasma FD/V and the over-all elimination constant K. It was impossible to get reliable estimates of k, since most of the experimental data refer to minimum plasma concentrations. However, k was found to be much larger than K in all cases, indicating that the rate of absorption had little influence.