Deterioration of kidney function by high doses of co-trimoxazole in man


Introduction

It has been frequently reported that long-term treatment with high doses of co-trimoxazole caused an increase in serum creatinine concentrations, due to a deterioration of kidney function. However, Kastrup et al. found no change in glomerular filtration after treatment with co-trimoxazole, but a decrease in creatinine clearance of 25% with trimethoprim alone. If a decrease in creatinine clearance reflects deteriorating kidney function, then renal clearance of the causative agents should also decrease. Ideally to assess the effects of co-trimoxazole on creatinine clearance, blood and urine samples must be collected over a long period and renal clearance values of all the compounds involved (creatinine, parent drugs and metabolites) calculated.

The opportunity arose to observe the deterioration of kidney function as expressed by a decrease in renal clearance values of creatinine, sulfamethoxazole, trimethoprim and metabolites, in a patient who was treated during three weeks with high doses of co-trimoxazole because of a Pneumocystis carinii infection.

Methods

PATIENT

A 40 year old male was admitted to the hospital with shortness of breath at rest, a non-productive cough and fever. Nine years earlier he received a cadaveric kidney graft because of end-stage renal failure due to chronic pyelonephritis. His immunosuppressive regime consisted of prednisone 10 mg and ciclosporin A 5 mg/kg. Physical examination revealed cyanosis and rales over both lung fields. X-ray examination of the lungs showed a diffuse reticulo-nodular infiltrate. Arterial blood gas analysis showed an evident hypoxaemia of 6.8 kPa. Pneumocystis carinii infection was suspected and confirmed with a thorascopic lung biopsy, which was necessary since bronchoscopic investigation was negative.

Co-trimoxazole treatment was initiated in a dose of four tablets four times a day. Because of too high blood concentrations, it was stopped after 48 h and restarted after 150 h in a dose of four tablets four times a day. The dose was lowered to three tablets four times a day due to nausea, and after 450 h to one tablet four times a day. Because of pancytopenia treatment was discontinued again after nineteen days. Finally the patient became free of symptoms with a complete resolution of the X-ray abnormalities.

DRUGS

Co-trimoxazole (Bactrim®), sulfamethoxazole and trimethoprim were obtained from Hoffmann-La Roche (Mijdrecht, The Netherlands), 5-hydroxysulfamethoxazole and N4-acetyl-5-hydroxysulfamethoxazole were isolated from the urine of dog and goat. N4-acetyl-sulfamethoxazole was synthetized as previously described.

ANALYSIS

5 ml Venous blood samples were collected at several intervals during the period of treatment. After centrifu-
gation plasma samples were stored at −20°C pending analysis.

Urine was collected over periods of 12 h throughout the 500 h period. Urinary pH was measured immediately after collection, using a Radiometer (PMH61; Radiometer, Copenhagen, Denmark) instrument. Urine samples of 10 ml were stored at −20°C pending analysis.

Trimethoprim, sulfamethoxazole and its 5-hydroxy and N4-acetyl metabolites were measured by an HPLC method as previously described.18 19

RENAL CLEARANCE
The apparent and true renal clearance values of trimethoprim, sulfamethoxazole and its 5-hydroxy and N4-acetyl metabolites were calculated by dividing the average renal excretion rate in each urine sample by the plasma concentration at the midpoint of the measured time interval. To calculate the apparent renal clearance values, the total plasma concentration was used; for the true renal clearance values, the free or unbound plasma concentration was used.

STATISTICS
Regression lines, standard deviations and correlation coefficients were calculated with an HP 33 or HP 41 calculator (Hewlett Packard, Amstelveen, The Netherlands). The Kruskal-Wallis test for parallel independent groups was carried out by means of the Statistical Analysis Systems (SAS). The Wilcoxon test was used to calculate statistical significance (p < 0.05).

Results
Figure 1 shows the plasma concentration–time curves of creatinine, trimethoprim (TMP), sulfamethoxazole (S) and the metabolites 5-hydroxysulfamethoxazole (SOH), N4-acetylsulfamethoxazole (N4), and N4-acetyl-5-hydroxysulfamethoxazole (N4OH) in a patient treated for Pneumocystis carinii with a high dose of co-trimoxazole. The second treatment period (150-500 h) is shown.

The dosage was reduced to three tablets four times a day and at 450 h to one tablet four times a day. The steady-state plasma concentration of sulfamethoxazole was 320 μg/ml, that of trimethoprim 15 μg/ml (a ratio of 21:1). The creatinine plasma concentration rose from 280 μmol/l (at 180 h) to 340 μmol/l (at

FIGURE 1
Plasma concentration–time curves of creatinine, trimethoprim (TMP), sulfamethoxazole (S) and the metabolites 5-hydroxysulfamethoxazole (SOH), N4-acetylsulfamethoxazole (N4), and N4-acetyl-5-hydroxysulfamethoxazole (N4OH) in a patient treated for Pneumocystis carinii with a high dose of co-trimoxazole. The second treatment period (150-500 h) is shown.

FIGURE 2
Renal clearance–time profiles of creatinine, sulfamethoxazole (S) and 5-hydroxysulfamethoxazole (SOH). The whole period of sampling (0-500 h) is shown.