Renal Tolerance of Cefpirome (HR 810), a New Cephalosporin Antibiotic

Summary: An open study was carried out in ten healthy, male volunteers in order to investigate the renal tolerance of cefpirome (HR 810), a new cephalosporin antibiotic. Subjects received a single dose of 1.0 g of cefpirome and then repeated doses of 1.0 g of cefpirome twice daily for five days. Urine was collected in several fractions during the study and the urine excretion, excretions of creatinine, N-acetyl-β-D-glucosaminidase, gamma glutamyltransferase, alanine aminopeptidase and lactate dehydrogenase were calculated in 12-hour fractions. Serum creatinine (using an enzymatic method), β₂-microglobulin concentrations and creatinine clearance were also determined. Based on the findings of these renal enzymes, renal tolerance was good. This was also confirmed by creatinine clearance calculations and follow-up of serum β₂-microglobulin levels. Cefpirome showed good renal tolerance without any signs of nephrotoxicity in this study with the methods used.

Introduction

Cefpirome (HR 810) is a new cephalosporin derivative with a broad antibacterial spectrum (1). Earlier studies have shown a dose-linearity within the dose range from 0.25 g to 2.0 g regarding AUC₀₋₂₄ and urinary excretion (Maaß, L., et al.: this issue p. 202). It has also been shown that the bioavailability of cefpirome is equal after intramuscular and intravenous administration (Maaß, L., et al.: this issue p. 207). There were no indications of drug accumulation when applied in the tested dose of 1.0 g b.i.d. for five days (Malerczyk, V., et al.: this issue p. 211). The half-life of cefpirome is about 2 h, and about 80% of the drug is excreted unchanged through the kidneys.

Nephrotoxicity as a consequence of treatment with some cephalosporins is well documented in animals and human beings, especially for cephaloridine (2). Cephalothin may also be nephrotoxic (3, 4). The primary target of cephalosporins in the kidneys is the lysosomal system (5).

The value of urinary enzymes for revealing early kidney damage is gaining more and more attention. The enzymes are very sensitive indicators of kidney damage, especially if several enzymes are assayed simultaneously and the activities of these enzymes are high in different regions of the nephron (6). Enzyme activity in urine is normally low. The changes in urinary profiles support the interpretation of kidney damage, especially when patients with non-renal disease or volunteers with normal kidney function are given new drugs with questionable nephrotoxic properties. Urinary enzymes reflect the metabolic state of renal tubular cells. One should therefore find diminished urinary enzyme activities in severely damaged kidneys, or small but significant rises in enzyme activity following chronic or long term kidney damage (7).

Recording the urinary excretion of the enzymes N-acetyl-β-D-glucosaminidase (NAG), gamma glutamyltransferase (GGT), alanine aminopeptidase (AAP) and lactate dehydrogenase (LDH) appears to be worthwhile because the primary target of cephalosporins in the kidneys is the...
lysosomal system. The excretion of NAG correlates most closely to the damage produced by antibiotics (8, 9), but also increases of GGT (10), AAP and LDH have been described (10, 11).

β₂-microglobulin in serum is also being used as an indicator of nephrotoxicity. It is a low molecular protein situated on the cell surface. It is exclusively eliminated through the kidneys, where it undergoes glomerular filtration and is subsequently reabsorbed and metabolized in the tubuli (12-14). The serum levels of β₂-microglobulin correlate better with the glomerular filtration rate than those of creatinine (13, 15) and an even slight reduction in the glomerular filtration rate is reflected by this variable. Therefore, follow-up of kidney function by assessing β₂-micro-

Figure 1: Measurement of urinary excretion of N-acetyl-β-D-glucosaminidase (NAG) during the single and multiple dose phases: median values from urine fractions of ten subjects.

Figure 2: Measurement of urinary excretion of gamma glutamyltransferase (GGT) during the single and multiple dose phases: median values from urine fractions of ten subjects.

Figure 3: Measurement of urinary excretion of alanine aminopeptidase (AAP) during the single and multiple dose phases: median values from urine fractions of ten subjects.