POSSIBLE INVOLVEMENT OF P-GLYCOPROTEIN IN RENAL EXCRETION OF PAZUFLOXACIN IN RATS

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The present study aims to investigate whether pazufloxacin (PZFX), a new quinolone, is a substrate for P-glycoprotein (P-gp), in vitro and whether it is excreted from kidney by P-gp and/or Mrp2 in vivo. The in vitro experiments showed that the intracellular accumulation of PZFX in adriamycin-resistant cancer cells (K562/ADR) overexpressing P-gp was significantly lower than that in K562/S cells not expressing Pgp. Cyclosporine (CyA) significantly decreased the systemic clearance and volume of distribution at steady state of PZFX to 50% and 70% of the corresponding control values, respectively. Renal handling experiments revealed that the renal clearance of PZFX was 75% of the corresponding to the systemic clearance, suggesting that the main route of PZFX elimination is the kidney. CyA significantly increased the steady-state concentration of PZFX in plasma by decreasing the tubular secretion clearance and GFR. These results suggest the possibility that PZFX is excreted into the urine via P-gp. No significant differences in the renal and tubular secretion clearances of PZFX were observed between normal rats and Eisai hyperbilirubinemic rats (EHBR) lacking Mrp2, indicating the lack of the involvement of Mrp2 in the renal excretion of PZFX. Sparfloxacin, a P-gp substrate, also significantly decreased the renal and tubular secretion clearances of PZFX, suggesting that PZFX and sparfloxacin share the same transporters, including P-gp. These findings suggest that PZFX is excreted into the urine via P-gp and some active drug transporters other than Mrp2.