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Pharmacokinetics of sunitinib in combination with fluoroquinolones in rabbit model

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Abstract:
Background: Fluoroquinolones are widely prescribed antibiotics. Ciprofloxacin is a well-known inhibitor of cytochrome P450 CYP3A4 and causes numerous drug interactions that are not found for levofloxacin and moxifloxacin. CYP3A4 is involved in the metabolism of the new oral multikinase inhibitor sunitinib which is indicated for the treatment of gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC). This study investigated the effects of single intravenous dose of ciprofloxacin, levofloxacin or moxifloxacin on the pharmacokinetics of sunitinib.
Methods: Rabbits were subjected to one of four study drug groups: sunitinib + ciprofloxacin (n = 6), sunitinib + levofloxacin (n = 6), sunitinib + moxifloxacin (n = 6), or sunitinib alone (n = 6). The rabbits were treated with sunitinib in the oral dose of 25 mg. The antibiotics were administered intravenously at the doses of 20, 25 and 20 mg/kg, respectively. Plasma concentrations of sunitinib and active metabolite (SU12662) were measured with validated HPLC method with UV detection.
Results: The comparison of sunitinib C_{max} for the sunitinib + ciprofloxacin, sunitinib + levofloxacin, sunitinib + moxifloxacin group and that for the sunitinib group gave ratios of 1.81 (90% CI 1.33, 2.44), 1.59 (90% CI 1.18, 2.16), 1.06 (90% CI 0.79, 1.44), respectively. The comparison of sunitinib $AUC_{0-\infty}$ for the sunitinib + ciprofloxacin, sunitinib + levofloxacin, sunitinib + moxifloxacin group and that for the sunitinib group gave ratios of 2.90 (90% CI 1.32, 6.37), 2.45 (1.11, 5.39), 1.58 (0.70, 1.56), respectively. The mean sunitinib t_{max} was similar for all four groups. The mean C_{max} for SU12662 was similar for both the sunitinib + moxifloxacin and sunitinib groups ($p = 0.9593$). However, the mean C_{max} for SU12662 for the groups: sunitinib + ciprofloxacin and sunitinib + levofloxacin were higher ($p = 0.0045$ and 0.0672, respectively).
Conclusions: The study proved a significant effect of the coadministration of ciprofloxacin and levofloxacin on the pharmacokinetics of sunitinib in rabbits. The influence of moxifloxacin on the pharmacokinetics of sunitinib was insignificant. Therefore, this fluoroquinolone seems to be the most appropriate in combination with this tyrosine kinase inhibitor.

Key words:
sunitinib, SU12662, fluoroquinolones, pharmacokinetics