195 Association between CYP3A enzyme activity and ciprofloxacin and clarithromycin pharmacokinetics in patients with cystic fibrosis

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Background: Human cytochrome P450 (CYP) 3A enzymes play an important role in drug metabolism. The in vivo activity of CYP3A varies 40-fold. Ciprofloxacin (CIP) and clarithromycin (CLA) are partly metabolised by CYP3A. The aim of this study was to investigate the pharmacokinetics of CIP and CLA in patients with cystic fibrosis (CF), and the association to CYP3A activity.
Methods: Nine CF patients were included in the study. CYP3A activity was measured by erythromycin breath test (ERMBT). Plasma concentrations of CIP and CLA were measured at 0, 30, 45, 60, 90, 120 minutes, and 3, 6, 12 hours after oral administration of 500 mg CIP and 500 mg CLA.
Results: The variability of CYP3A activity (ERMBT, %14C/h) was 4-fold (range 0.25–1.0). Table 1 shows the pharmacokinetics of CIP and CLA. AUC of CLA showed great variation with 8-fold difference between the highest and the lowest value (436–3435 ug/ml x min). There was only 1.5-fold difference between the highest and the lowest AUC of CIP (331–520 ug/ml·min). No significant correlation between CYP3A activity and AUC of CIP and CLA could be demonstrated by linear regression analysis.
Conclusion: There was a large variation in CIP and CLA pharmacokinetics in our patients. The variation was not explained by CYP3A activity. Further data analysis by the use of multivariate methods and inclusion e.g. absorption and concomitant drug use may clarify our findings.

	AUC (ug/ml·min)	Cmax (ug/ml)	Tmax (min)
Ciprofloxacin	409±71	1.65±0.67	67±27
Clarithromycin	1355±1052	4.64±3.32	112±103

Values are mean±SD.

196 Pharmacokinetics and antibacterial activity of inhaled liposomal ciprofloxacin hydrochloride in healthy volunteers and in cystic fibrosis (CF) patients

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Inhaled Liposomal Ciprofloxacin Hydrochloride (ILCH) is being developed for the management of P. Aeruginosa (PA) infections in cystic fibrosis (CF) patients. Three doses of ILCH were studied in healthy volunteers to determine safety, tolerability and pharmacokinetics (PK), as single doses of 3, 6 and 9 mL of the 50 mg/mL formulation via a nebulizer. Additionally 8 subjects inhaled the 6 mL dose once daily for 7 days. The formulation was safe and well tolerated. Plasma PK profile of the single and multiple doses showed sustained release of ciprofloxacin from the liposomes over 24 hours with an absorption-limited half life ($T_{1/2}$) of ~10.5 hours, compatible with a single daily dosing regimen. A Phase 2 study (n = 22) to evaluate the safety, tolerability, PK and effect on sputum PA density following 14 consecutive days of 6 mL once-daily nebulized ILCH in adult CF patients was conducted. The drug was well tolerated with no serious adverse events. There was a mean decrease of 1.43 log10 colony forming units (CFU) in sputum density of PA after 14 days of treatment ($p < 0.01$) with the mean CFU still reduced by 1.03 log10 a week after treatment was stopped. Mean FEV1 increased by 6.9% from baseline ($p = 0.04$) after 14 days of treatment. The PK parameters observed in the CF patients were similar to those in healthy volunteers. High concentrations of ciprofloxacin were found in sputum. The sustained release profile of ILCH and its effect in reducing PA sputum density support further clinical development of the product.
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