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MEETING ABSTRACT

A2.1

Biliary amphotericin B pharmacokinetics and pharmacodynamics

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Background: Fungal cholangitis is a life-threatening condition affecting mainly immune-compromised persons, patients with choledocholithiasis, cancer, bile duct strictures, primary sclerosing cholangitis and liver transplant recipients. Because of its broad fungicidal activity, amphotericin B (AMB), particularly less toxic lipid-formulated AMB, is a therapeutic option. Therefore, biliary penetration of AMB was determined in four patients treated with AMB lipid formulations. Activity of AMB in bile at therapeutically achievable concentrations was assessed by *in vitro* simulation in order to detect an eventual ambience effect.

Methods: Two patients received liposomal AMB, two patients AMB colloidal dispersion. AMB concentration–time profiles in bile and plasma were determined in three liver transplant recipients. Bile was collected via T-tube or bile duct drainage. In addition, one sample was obtained by endoscopy from a fourth patient. The samples were purified by solid phase extraction. AMB was extracted with dimethyl sulfoxide and methanol and quantified by high-pressure liquid chromatography (HPLC). *In vitro* simulation was performed with isolates of *Candida albicans*, *C. tropicalis*, *C. glabrata* and *C. krusei* incubated with AMB at concentrations of 0.025, 0.05, 0.10, 1.00 and 5.00 mg/l, respectively, dissolved in porcine bile, RPMI medium and RPMI medium at pH 7.8. Inocula of 10,000 cells of each *Candida* strain were incubated for 0, 7, 12, 24 and 48 hours, seeded by a spiral platter and manually counted.

Results: Biliary AMB concentrations (maximum 1.28 mg/l) were lower and displayed a slower rise and decline in comparison with plasma levels. The highest penetration ratio as expressed by the ratio between the area under the time–total-AMB-concentration curve in bile and plasma over the sampling period ($AUC_{0–n\ bile}$ / $AUC_{0–n\ TO\ plasma}$) amounted to 0.14. *C. albicans* and *C. tropicalis* presented a proliferation in bile similar to that in RPMI media whereas colony forming units (CFU) of *C. krusei* and *C. glabrata* remained constant over 48 hours. A biliary AMB concentration of 1 mg/l or less was not effective against the four *Candida* strains. Even the highest AMB concentration (5.00 mg/l) which exceeds biliary concentrations measured in our patients did not cause a relevant decline in CFU. Thus, AMB activity in porcine bile was lower than in culture medium.

Discussion: In the majority of bile samples, AMB concentrations were similar to or even markedly below the *in vitro* MIC values reported for relevant pathogens. *In vitro* simulation revealed a decreased antifungal activity of AMB in bile in comparison with RPMI suggesting an ambiance effect of bile on AMB pharmacodynamics. Based on these data, a reliable response of fungal cholangitis to treatment with AMB lipid formulations cannot be anticipated.

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