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P0117 Pharmacokinetics of posaconazole in adult obese patients and normal-weight patients

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Background: One in five individuals will be obese in 2025. Obese patients are at risk for underdosing of antimicrobial drugs in prophylaxis and treatment of (life-threatening) infections. Posaconazole is a triazole broad-spectrum antifungal drug frequently used for prophylaxis and treatment of mold infections. There is anecdotal evidence that posaconazole exposure is impacted by weight resulting in suboptimal target attainment (PTA) in obese individuals. We performed a prospective clinical trial to investigate the effect of body size in (morbid) obese subjects and determined the chance of reaching the target trough concentration for prophylaxis (0.7 mg/l) and therapy (1 mg/l).

Materials/methods: Morbidly obese subjects (BMI>35kg/m^2) undergoing bariatric surgery and normal-weight subjects (BMI 18.5-25kg/m^2) were included in an open-label, single-dose, multicenter, multi-dose level, pharmacokinetic study. Obese subjects were randomized to receive either 300 or 400 mg posaconazole IV while normal-weight subjects received 300mg posaconazole IV. Blood samples were collected at 9 time points up to 24 hours after start infusion. Statistical and population pharmacokinetic analysis was performed using R and NONMEM 7.3.

Results: 8 obese subjects on 300mg, 8 obese subjects on 400mg and 8 normal-weight subjects were included. Weight [range] was 129 [109-190]), 144 [107-175]), 72.3 [61.4-85.4]kg respectively.

The observed geometric mean [range] AUC0-24h in normal-weight versus obese subjects receiving 300mg posaconazole was 21.4 mg*h/L [15.6-29.1] versus 13.1 mg*h/L [9.1-18.5] ($p<0.05$). A two-compartment model with first-order elimination, a proportional residual error model and inter-individual variability on the central compartment (Vc) best described the data. Obese subjects receiving 400mg posaconazole had an AUC0-24h of 16.8 mg*h/L [12.2-25.6]. Simulations demonstrated that in the treatment of mold infections, a 300 mg dose is sufficient up to 120 kg after which a dose increase to 400 mg daily is needed to result in a >90% PTA (1.0 mg/L as target). For prophylaxis, no dose adjustments are needed to attain >90%PTA up to 190 kg.

Conclusions: We found that obese individuals have a significant lower exposure to posaconazole compared to normal-weight individuals. Nevertheless, PTA (at 0.7mg/L) was high using the IV formulation. For posaconazole treatment (PTA 1.0mg/L) higher dosages are warranted in obese subjects.