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ORLISTAT TREATMENT DECREASES PLASMA BILIRUBIN CONCENTRATION IN GUNN RATS BY INCREASING TURNOVER OF BILIRUBIN**Anja M. Hafkamp¹, Rick Havinga¹, Lorella Pascolo², and Henkjan J. Verkade¹**¹ Department of Pediatrics, University Hospital Groningen, Groningen, The Netherlands;² CSF and Department of Biochemistry, Biophysics and the Chemistry of Macromolecules, University of Trieste, Trieste, Italy.

Background: Previously, we showed in the Gunn rat model of unconjugated hyperbilirubinemia that dietary supplementation with the lipase inhibitor orlistat decreased plasma concentrations of unconjugated bilirubin (UCB), parallel to an increase in fecal fat excretion.¹ In Gunn rats, orlistat is equally effective as phototherapy in decreasing plasma bilirubin levels, and combined treatment is more effective than either treatment alone.² We hypothesize that orlistat enhances turnover and fecal excretion of bilirubin.

Objective: To determine the effects of orlistat and phototherapy on ³H-bilirubin turnover.

Methods: Adult male Gunn rats (n=4-6 per group) were either not treated (controls), or treated for 3 weeks with dietary orlistat supplementation (200 mg/kg chow), continuous phototherapy (PT, 380-480 nm, 9 μW/cm²/nm), or both (orlistat+PT). After 3 weeks of treatment (T₀h), ³H-UCB (~0.5 μCi/100g BW; specific activity 48800 dpm/μg UCB) was administered i.v. to determine steady-state bilirubin turnover. Blood samples were collected via tail vein bleeding every 12h for 60 hours. After 60 hours, bile was collected for 30 minutes after cannulation of the common bile duct. Feces were collected every 12h for 60 hours to determine fecal ³H loss. Plasma total bilirubin concentration was determined by a routine chemical procedure. Biliary UCB concentration was determined by HPLC. ³H in plasma, bile and feces was determined by liquid scintillation. Fractional turnover of ³H-UCB (%/h) was calculated from plots of ³H-UCB specific activity vs. time. Bilirubin pool size (mg/100g BW) was calculated using the Y axis intercept from these plots.

Results: After 3 weeks of treatment (T₀h), orlistat had decreased plasma total bilirubin concentrations, compared with controls (μmol/l; mean±SD; 301±43) by 19% (243±23, p<0.05), PT by 32% (206±38, p<0.01) and orlistat+PT by 53% (143±12, p<0.001). Combined treatment with orlistat+PT was more effective than either orlistat (p<0.001) or PT (p<0.05). Between T₀h and T₄₈h plasma bilirubin levels were stable, indicating steady-state conditions. Fractional turnover (%/h) of ³H-UCB was 1.4±0.8 in controls, 2.4±0.7 in orlistat (+69%, p=0.07), 2.8±0.4 in PT (+101%, p<0.05), and 4.2±0.6 in orlistat+PT (+198%, p<0.001). There was a negative linear correlation between plasma bilirubin concentrations at T₀h and fractional turnover of ³H-UCB (r=-0.90, p<0.0001). Biliary UCB output (nmol/h/100g BW) was 29±4 in controls, 26±7 in orlistat (-12%, NS), 37±6 in PT (+25%, NS), and 20±7 in orlistat+PT (-33%, p<0.05). Bilirubin pool sizes (mg/100g BW) were 2.8±0.7 in controls, 2.2±0.3 in orlistat (-23%, p=0.09), 2.0±0.3 in PT (-28%, p=0.07), and 1.6±0.1 in orlistat+PT (-45%, p<0.01). Between T₃₆h and T₄₈h, fecal ³H excretion was 110% higher in orlistat treated rats, compared with controls (p<0.05).

Conclusions: Orlistat treatment decreases plasma bilirubin concentration in Gunn rats by increasing turnover and fecal excretion of bilirubin. The therapeutic effect of orlistat can be enhanced by phototherapy. Present data indicate that orlistat, alone or in combination with phototherapy, could be an effective treatment for unconjugated hyperbilirubinemia (Crigler-Najjar disease, neonatal jaundice).

References

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Orlistat treatment increases fecal bilirubin excretion and decreases plasma bilirubin concentrations in hyperbilirubinemic Gunn rats. *J Pediatr* 2003;143(3):327-334.

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