Oral treatment of unconjugated hyperbilirubinemia
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Outline of this thesis

CHAPTER 2

[Chemical structure diagram]
Chapter 2

OUTLINE OF THIS THESIS

This thesis focuses on oral treatment of unconjugated hyperbilirubinemia. Permanent unconjugated hyperbilirubinemia occurs in patients with Crigler-Najjar disease due to a genetic deficiency of the hepatic enzyme bilirubin-UDP-glucuronosyltransferase (UGT1A1). Glucuronidation of unconjugated bilirubin (UCB) via UGT1A1 greatly enhances its biliary secretion and subsequent fecal excretion. Accumulation of UCB in the body can cause bilirubin-induced neurologic damage and kernicterus, resulting in physical and mental handicaps or even death. Conventional treatment for Crigler-Najjar disease involves daily phototherapy for up to 12 hours. Long-term daily phototherapy has considerable disadvantages. Main problems are a decreasing efficacy with age and a profound impact of the intensive phototherapy regimen on the quality of (social) life.

We aimed to develop an alternative or additional treatment for unconjugated hyperbilirubinemia in Crigler-Najjar disease that is based on oral administration. The oral treatment approach is based on previously demonstrated strategies for intestinal capture of UCB (Figure 1). Particularly when plasma UCB levels are high as in Crigler-Najjar disease, UCB can diffuse from the blood into the intestinal lumen across the intestinal mucosa. In addition, under conditions of absent or strongly diminished conjugation, small amounts of UCB enter the intestine via biliary secretion. Intestinal capture of UCB followed by enhanced fecal excretion has been shown to reduce the enterohepatic circulation of UCB and to decrease plasma UCB concentration. Binding of UCB in the intestine increases the gradient for unbound UCB from blood to intestinal lumen, enhancing transmucosal diffusion.

Considering the relatively lipophilic character of UCB, we hypothesized that UCB could associate with (unabsorbed) fat in the intestine, although no direct evidence exists for

Figure 1. Intestinal capture of UCB. A: In Crigler-Najjar disease, UCB can enter the intestine via biliary secretion and via transepithelial diffusion from the blood into the intestinal lumen, across the intestinal mucosa. UCB and its metabolites are partly excreted with the feces, and partly reabsorbed into the enterohepatic circulation (EHC). B: Capture of UCB in the intestine followed by enhanced fecal excretion reduces the enterohepatic circulation of UCB. Binding of UCB in the intestine increases the gradient for unbound UCB from blood to intestinal lumen, enhancing transmucosal diffusion.
increased binding. In chapter 3 of this thesis we investigated whether stimulation of fecal fat excretion affected plasma UCB concentrations in Gunn rats. The Gunn rat is a well-established animal model for permanent unconjugated hyperbilirubinemia (Crigler-Najjar disease type I). Fecal fat excretion was increased by dietary supplementation with the lipase inhibitor orlistat. Orlistat inhibits intestinal hydrolysis of dietary triglycerides and thereby reduces dietary fat absorption. Gunn rats received short-term (≤3 weeks) or long-term (24 weeks) orlistat treatment. Effects of orlistat treatment on plasma UCB concentrations and on fecal excretion of fat and UCB were determined.

In chapter 4 we compared the effects of orlistat treatment with the effects of a previously demonstrated oral treatment for unconjugated hyperbilirubinemia, calcium phosphate. Calcium phosphate treatment had effectively reduced plasma UCB levels in Gunn rats, but efficacy was less pronounced in patients with Crigler-Najjar disease. We determined the separate and the combined effects of orlistat and calcium phosphate treatment on plasma UCB concentrations in Gunn rats. Also, we compared the efficacy of orlistat and/or calcium phosphate with the conventional treatment for unconjugated hyperbilirubinemia, phototherapy. To determine whether the effects of orlistat and calcium phosphate were influenced by dietary fat content, we conducted our experiments during a low-fat and high-fat diet.

In chapter 5 we investigated in Gunn rats the mechanism(s) underlying the effects of orlistat, phototherapy and of combined treatment on UCB homeostasis. Using $^{3}$H-UCB kinetics we determined the effects of the three treatments on fractional turnover of UCB, and on biliary secretion and net transmucosal excretion of UCB. We developed a new method of estimating the steady-state enterohepatic circulation and intestinal flux of UCB and its derivatives.

Chapter 6 describes the effects of orlistat treatment on plasma UCB concentrations in patients with Crigler-Najjar disease. A randomized placebo-controlled cross-over trial was conducted in 16 patients, simultaneous with their regular treatment with phototherapy and/or phenobarbital. Patients received orlistat or placebo, each for 4-6 weeks with 2 weeks interval. We determined the effects of orlistat treatment on plasma UCB concentrations and on fecal excretion of fat and UCB.

In chapter 7 we performed initial experiments towards another strategy for oral treatment of unconjugated hyperbilirubinemia. The bile salt ursodeoxycholic acid (UDCA) had been suggested to impair fat absorption. Since our previous studies indicated that stimulation of fecal fat excretion decreased plasma UCB concentrations, we investigated in Gunn rats whether dietary supplementation with UDCA or with a different bile salt, cholic acid (CA), affected plasma UCB concentrations and fecal excretion of fat and UCB.

Chapter 8 provides a summary and general discussion of the research described in this thesis, including conclusions and perspectives for future studies.
REFERENCES