The Effect of Cisapride on Total Parenteral Nutrition-associated Cholestasis in Rats

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Abstract

Background: Cholestasis is a frequent problem in patients on total parenteral nutrition. Cisapride has a prokinetic effect on the biliary system, but its effect on hepatic excretory function is unknown.

Objectives: To study the effect of cisapride on TPN-induced cholestasis in a rat model.

Methods: Bile flow and bile salt secretion rate were measured in rats given TPN. There were four groups of 8 to 13 animals each. After a one hour baseline period during which all four groups received i.v. saline infusion, two groups received a TPN solution for another 2 hours, while saline was infused in the two control groups. At the beginning of the second hour, 2 mg/kg cisapride was injected i.v. as a bolus into one experimental and one control group. Bile was collected from the common bile duct.

Results: At the end of the third hour, TPN caused a significant reduction in bile flow ($P<0.02$) and bile salt secretion rate ($P<0.001$) (61.24 vs. 50.74 μl/min/kg, and 1.173 vs. 0.799 μmol/min/kg, respectively). Addition of cisapride abolished the cholestatic effect of TPN.

Conclusions: Cisapride has a protective effect against TPN-associated cholestasis. This may have clinical significance, and further studies are warranted.

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Total parenteral nutrition-associated cholestasis is common in children and adults [1,2]. The mechanism of action is most probably multifactorial and involves, among others, lack of enteral feeds, amino acids, caloric excess, and sepsis. Alterations in bile salt concentrations and in liver morphology have also been described [2–6].

Cisapride is a gastrointestinal prokinetic agent that is currently used widely to treat motility disorders such as gastro-esophageal reflux, gastroparesis, functional dyspepsia and constipation [7]. Cisapride affects gallbladder contractility [8,9] and leads to a normal bile salt profile in an animal model of gallstone disease [10]. Improvement of gallbladder contractility is seen in patients with myotonic muscular dystrophy [11], gallbladder hypokinesia [12], diabetes mellitus [13] and postcholecystectomy syndrome treated with cisapride [14]. Cisapride also increases bile flow due to relaxation of the sphincter of Oddi [15,16].

The aim of our study was to evaluate the effect of cisapride on TPN-associated cholestasis in rats.

Methods

Bile flow and bile salt secretion were measured in 24 hour fasted male Wistar rats weighing 250–300 g as previously described by us [17]. Animals were anesthetized with 50 µg/kg intraperitoneal injection of Nembutal (Abbot, Belgium). The airway was protected by tracheostomy and body temperature was maintained by an external heat source.

Bile was collected from a catheter inserted into the common bile duct every 20 minutes for 3 hours. During the second and third hour, taurocholic acid (Calbiochem-Behring Corp., Germany), the main bile acid in rats, was infused at 10 μmol/min/kg to maintain bile secretion. Bile flow was determined at 15 min intervals and bile salt concentration in bile was measured enzymatically [18].

Four groups of 8–13 animals each were studied, and all received saline infusion during the first baseline hour. Two groups received a TPN solution at a rate of 10 ml/kg/h for an additional 2 hours, and the control groups received a similar volume of saline infusion. Cisapride (Janssen-Cilag, Israel), 2 mg/kg, was injected as a bolus i.v. at the beginning of the second hour into one experimental and one control group of animals.

The TPN solution was made with Travasol 2.5% (Baxter Travenol Laboratories, Israel), glucose 10%, and electrolytes. Every 1,000 ml of TPN solution [17] contained dextrose 320 g, nitrogen 8 g, sodium 100 mEq, potassium 60 mEq, chloride 90 mEq, calcium 0.2 g, phosphorous 0.01 g, and magnesium 0.02 g. Caloric density was 1.48 Kcal/kg/24 h and 10 ml/kg/h provided 355 Kcal/kg/24 h, which is in accordance with the daily caloric requirement of the rat [19]. Results were expressed as the mean±SD.

Student's *t*-test (unpaired) was used to evaluate differences between the various means.

TPN = total parenteral nutrition

Results

The results are shown in Tables 1 and 2. Compared to controls, administration of TPN led to a significant reduction of bile flow, 50.74±15.52 vs. 61.24±20.01 μl/min/kg (mean±SD, $P<0.025$). Cisapride alone had no effect on bile flow (68.10±19.20 μl/min/kg, not significant vs. controls), but the addition of cisapride to TPN abolished the reduction of flow caused by TPN, 65.02±11.93 vs. 50.74±15.52 μl/min/kg (mean±SD, $P<0.005$).

Bile salt secretion rate was also significantly reduced by TPN infusion, 0.799±0.3 vs. 1.173±0.388 μmol/min/kg (mean±SD, $P<0.001$). This effect was abolished by the addition of cisapride, 1.044±0.137 vs. 0.799±0.3 μmol/min/kg (mean±SD, $P<0.001$). Cisapride alone had no effect on BSSR.

Discussion

TPN reduces bile flow and bile salt secretion rate. We previously showed this effect even after short-term infusion of 3 hours [3,17]. The pathogenesis is multifactorial and is related to prematurity, low birth weight, and duration of TPN [5,6]. Biliary stasis may be an important mechanism in the development of cholestasis [6].

Our results demonstrate that while cisapride has no effect on bile flow and BSSR in the intact rat, it abolishes the cholestatic effects of TPN. The dose of cisapride that we used is high, but even much higher doses have been frequently used in animal studies. Preliminary studies in our laboratory suggested use of this dose in order to maximize the effects of cisapride.

Cisapride acts as a postganglionic serotonin 5-HT4 receptor agonist. It enhances release of acetylcholine in the myenteric plexus, thus accounting for its activity as a gastrointestinal prokinetic drug [20].

There is little information on the effect of cisapride on the biliary tract and the liver. In animals and humans it has been shown to improve gallbladder contractility [12,16]. In isolated guinea pig gallbladder and common bile duct preparations, cisapride stimulated motility, which was probably of cholinergic origin [21].

Cisapride has been shown to reduce sphincter of Oddi basal tone. The inhibitory effect on the sphincter of Oddi may increase blood flow [15,16], which partially explains our results on bile flow.

Cisapride has also been shown to have an effect on water and electrolyte secretion in the intestinal tract. In rats whose colon was instilled with sodium acetate, cisapride induced an increase in sodium absorption and a reduction in water absorption [22]. In rat jejunum and ileum, cisapride induced water and electrolyte secretion, and slightly inhibited serotonin-induced secretory fluxes [23]. Stimulation of pancreatic secretion by cisapride has also been demonstrated [24]. Bile duct cells play an important role in maintaining, modifying and augmenting bile flow, and acetylcholine affects rat cholangiocyte secretory function [25].

The studies cited above may partially explain our results showing a reversal of TPN-induced reduction of BSSR. In the intact animal, regulatory mechanisms may counteract the effects of cisapride on bile flow and secretion. During TPN-induced cholestasis, some of these regulatory mechanisms may become inactivated, thus allowing the effect of cisapride to become evident, abolishing the cholestatic effect of TPN.

In conclusion, cisapride has been shown to reverse the cholestatic effect of TPN. This is probably due to a combination of its action on biliary tract motility and secretion. Both effects are probably mediated through release of acetylcholine. Further studies on its mechanism of action and possible clinical application during TPN are warranted.

Table 1. Effect of TPN and cisapride on bile flow

Group	Saline (n=13)	Saline + Cisapride (n=8)	TPN (n=12)	TPN + Cisapride (n=11)
Bile flow (μl/min/kg ±SD)	61.24±20.01	68.10±19.20	50.74±15.52	65.02±11.93
P value		NS vs. saline	<0.025 vs. saline, <0.005 vs. cisapride	NS vs. saline <0.005 vs. TPN

Table 2. Effect of TPN and cisapride on BSSR

Group	Saline (n=13)	Saline + Cisapride (n=8)	TPN (n=12)	TPN + Cisapride (n=11)
BSSR (μmol/min/kg ±SD)	1.173±0.388	1.231±0.342	0.799±0.300	1.044±0.137
P value		NS vs. saline	<0.001 vs. saline or cisapride	NS vs. saline <0.001 vs. TPN

BSSR = bile salt secretion rate

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It is better to fail in originality than to succeed in imitation.

Herman Melville

Capsule

Surgery and risk of HCV

In a case-control study carried out in Italy, participants were followed at 10 liver or gastroenterologic units and included 294 subjects with chronic HCV infection and 295 age- and sex-matched anti-HCV-negative controls. According to the results the use of glass syringes and surgical procedures was reported by as many as 77.6% and 73% of cases, respectively. Blood transfusion was recorded in nearly a quarter of the cases; and 10.2% of the cases — but none of the controls — reported past or current intravenous drug use. Multiple logistic regression analysis showed that blood transfusion, surgery, and being the sexual partner of an intravenous drug user, were independent predictors of the likelihood of HCV infection.

Given that a large proportion of the general population undergoes surgery, a rational and relatively inexpensive policy for the prevention of HCV infection must focus on implementing efficient procedures for the sterilization of instruments and the use of disposable materials in surgical units.

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