Experimental study of cholagogic cream for refractory jaundice

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Subject headings jaundice; cholagogic cream bile duct stenosis; cholestatic hepatitis

INTRODUCTION
“The refractory jaundice” in this paper implies the benign icteric disease which was repeatedly treated with either western or traditional Chinese medicine but gave no evidence of improvement, mainly including primary sclerosing cholangitis, intrahepatic sand-like calculi, bile duct stenosis and cholestatic hepatitis etc[1,2]. Such diseases are difficult to treat by both traditional Chinese and western medicine. In this study, the cholagogic and anti-inflammatory effects of cholagogic cream, and the combined effects with trepibutone on refractory jaundice were observed and evaluated by experimental pathologic and biochemical examination.

MATERIALS AND METHODS

Ingredients of cholagogic cream
Dandelion herb 20 g, curcuma root 15 g, Fructus Aurantii 10 g, Sichuan chinaberry 10 g, oriental wormwood 20g, lysimachia 20g, gentian root 10g, Chicken’s gizzard-skin-15 g, root bark of the tree peony 15 g, red peony root 15 g, red sage root 20 g, burreed tuber 15 g, zedoary 15 g, rhubarb 10 g, mirabilite 10 g, Herba Lycopi 15 g, earthworm 15 g.

Animal experiment
Thirty-two healthy adult hybrid dogs of either sex (mean weight, 18.1 kg) were selected. The animals were anesthetized intravenously with 2% pentobarbital sodium (30 mg/kg). Epigastric median incision was performed to reveal the common bile duct and hepatic porta. One percent formaldehyde solution was evenly and carefully infiltrated into the extrahepatic bile duct wall with a small needle. The volume depended on appearance of white on the bile duct wall. A mushroom like catheter (a catheter with a mushroom tip) was placed into the gallbladder, fixed on the abdominal wall, and the abdomen was closed after gastrostomy. The appearance of jaundice after one month indicated the success in model preparation.[2] The 32 dogs were randomly divided into control group, cholagogic cream group, trepibutone group, and cholagogic cream plus trepibutone group, 8 for each.

Route of drug administration
The medicine was administered through the gastrostomy tube, followed by 1/2 hour observation to make sure that no vomiting occurred.

The administration regimens (1 week) were:
Cholagogic cream plus trepibutone group: cholagogic cream 0.3 g/kg, twice a day; and trepibutone 0.75g/kg,three times a day.
Cholagogic cream group: cholagogic cream 0.3 g/kg, twice a day.
Trepibutone group: trepibutone 0.75 mg/kg, Three times a day.
Control group: normal saline 100 mL, twice a day.

Observation methods
The bile flow from the cholecystostomy tube in 24 hours was recorded at 08:00 every day, and 5 mL bile was taken for viscosity measurement. The remaining bile was trasfused bach to duodenum via the gastrostomy tube. The bile in the gallbladder was also collected regularly before and after operation for viscosity measur ement.

Changes of the serum total bilirubin, direct bilirubin and glutamic-pyruvic transminase were routinely detected.

The preparation and observation of the scanning electron microscopic sections were carried out in the Center for Computation and Test, Nankai University, Tianjin. Hitachi-650 scanning electron microscope was used, the maximal resolving power was 60A. The paraffin-embedded sections by routine HE staining were obse rved under optical micros-cope.
RESULTS
After therapy, the bile flow showed no significant change in the control group, but dramatically increased in trepibutone group and cholagogic cream group, especially in cholagogic cream plus trepibutone group.

The bile viscosity displayed no significant change in the control group, but dropped significantly in trepibutone group and cholagogic cream group, especially in cholagogic cream plus trepibutone group.

Serum total bilirubin and direct bilirubin were apparently decreased in all the groups except the control group.

Glutamic-pyruvic transaminase (GPT) was significantly decreased in all the groups, especially in cholagogic cream plus trepibutone group, except the control group.

Seven days later, the sections were observed under optical microscope. In the control group, inflammatory cell infiltration occurred in the bile duct wall, especially in the mucous submucous layers. In trepibutone group, inflammatory cell infiltration reduced, but the mucosal exfoliation was obvious. In cholagogic cream group, the inflammatory cells were decreased, and the endoscopic appearance of the gallbladder mucosa returned to normal. In cholagogic cream plus trepibutone group, the inflammatory cells were markedly decreased, and many new mucous membranes were observed.

The mucous membrane of the bile duct was observed under scanning electron microscope for 7 days. It was found that the mucosal membrane was swollen, and the microvilli were exfoliated from the surface of the mucosa in the control group. The edema was markedly alleviated, and the microvilli were quite rare in trepibutone group. A part of the microvilli appeared, and the edema was markedly reduced in cholagogic cream group. The edema was completely resolved and many neoformative microvilli were seen in cholagogic cream plus trepibutone group.

DISCUSSION
Sclerosing cholangitis, representative of the typical refractory jaundice clinically, served as the icterus model. This experiment found that cholagogic cream possesses a strong cholagogic effect (soothing the liver and normalizing the function of the gallbladder, eliminating blood stasis and removing obstruction in the meridians, and relieving jaundice), which results mainly from its ingredients such as dandelion herb, lysimachia, oriental wormwood, curcuma root, gentian root and rhubarb. The mechanism might be explained in two aspects. Cholagogic cream, on one hand, can promote the bile secretion from liver cells and bile capillaries, resulting in marked increase of bile flow, and sharp decrease of bile viscosity and serum total bilirubin; and on the other hand, it can also resolve mucosal edema in the bile duct and relax the sphincter, which can be explained by the observation under the scanning electron microscope and change of the serum direct bilirubin. Therefore, it is extremely beneficial to patients with refractory jaundice.

This experiment also proves that cholagogic cream has a strong anti-inflammatory effect (clearing away heat and toxic materials or expelling toxin by cooling, and promoting Qi flow and blood circulation). It could increase the phagocytosis of inflammatory cells by regulating the immunologic function, leading to the elimination of the inflammations in the liver cells and the bile duct wall, which can be proved by the sharp decrease of serum GPT level and the rapid resolution of the inflammation in bile duct wall observed under the optical microscope. The clinical experiences indicated that many refractory jaundices were mutually affected with other hepatic diseases, such as liver dysfunction, hepatic interstitial cells, the bile duct stenosis, edema and inflammation. So, we believe that the cholagogic cream possesses a unique advantage of overall regulation, which is absent in western medicine.

Besides, the combination of cholagogic cream and trepibutone can enhance the effects, the mechanism, beyond profound discussion here, might be complex, but it is certain that the combination of the traditional Chinese and western medicine for refractory jaundice is undoubtedly practicable.

REFERENCES
1 Huang ZQ. Primary sclerosing cholangitis. In: Wu JP, Qiu FZ, eds. Surgery of Huang Jiasi. 4th ed. Beijing: People’s Health Publishing House, 1979:1269-1271
2 Houry S. Sclerosing cholangitis induced by formaldehyde solution injected into the biliary tree of rats. Arch Surg, 1990;125:1059-1061
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