Hepatic and Pancreatic Metabolism and Biliary Excretion of the Protease Inhibitor Camostat Mesilate

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Summary

The hepatic metabolism and biliary and pancreatic excretion of the serine protease inhibitor camostat mesilate and its metabolites FOY-251 and GBA were studied in rats in vivo and in in situ liver-perfusion experiments. After oral feeding (100 mg/kg) and iv infusion (5 mg/kg·h) of camostat mesilate, the original compound and both metabolites appeared in bile, but could not be detected in pancreatic juice. In plasma, only FOY-251 and GBA were detected. In the perfused rat liver, camostat mesilate (10 μM) was eliminated by 33.8% and its molar rate of degradation to FOY-251 was 25.1%. During the study period about 0.10% of camostat mesilate and FOY-251 appeared in bile. The liver perfusion of FOY-251 or GBA revealed very low hepatic extraction rates of 10.3 and 2.4%, respectively. In conclusion, the low hepatic extraction rate of camostat mesilate and its metabolites leads to high concentrations of the active metabolite FOY-251 in plasma. Camostat mesilate and its metabolites are effectively excreted into bile, but not in rat pancreatic juice.

Key Words: Protease inhibitor; camostat mesilate; rat; liver in vivo; perfused liver; pancreatic juice.

INTRODUCTION

Camostat mesilate, a member of a new group of proteinase inhibitors that, chemically, are guanidino-esters, has a high binding affinity to trypsin, plasmin, kallikrein, thrombin, and esterolytic activities of the C1 esterases (1–3).
After oral administration, camostat mesilate is degraded rapidly by esterases and pH-dependent nonenzymatic hydrolysis into FOY 251, which retains the same binding specificity to serine proteases (4). FOY-251 is further converted to the guanidino benzoic acid that lacks protease inhibitor activity (4). In a recent study we found that hepatic elimination of camostat mesilate is low (5). It was hypothesized from this study that the low hepatic extraction of camostat mesilate leads to pharmacologically effective concentrations of the active metabolite FOY-251 in the circulation and possibly in biliary and pancreatic juice.

The aim of the present study was to analyze in rats whether, after hepatic extraction, camostat mesilate and its active metabolites are secreted into the bile and pancreatic juice and contribute to an enterohepatic circulation. This was studied in vivo by drainage of biliary and pancreatic ducts after oral or iv administration of camostat mesilate in conscious rats and in vitro by perfusing the in situ rat liver with camostat mesilate and its metabolites.

METHODS

Materials

All chemicals were reagent grade and from commercial sources. Enzymes and bovine serum albumin were purchased from Boehringer, Mannheim, FRG. Camostat mesilate (N,N-dimethyl carbonylmethyl-p-(p-guanidinobenzoxyloxy) phenylacetate methansulphonate) (Foipan), FOY-251, and GBA (p-guanidinobenzoate) were obtained from Schwarz Pharma, Monheim, FRG.

Animals

Male Wistar rats (180–240 g body wt) were obtained from Versuchstieranstalt, Hannover, FRG. They were kept on a 12-h day-night rhythm with free access to food and water. All experiments were started at 9 AM. The rats were anesthetized by ip injection of pentobarbital (60 mg/kg body wt).

In Vivo Procedures

Under anesthesia an upper abdominal wall incision was made in eight rats. After exposition of the duodenal loop the common bile–pancreatic duct was ligated close to its entry into the duodenum. A polyvinyl chloride cannula (0.75 mm od) was inserted proximal to the ligature. The bile duct was ligated at its point of entry into the pancreas and a second cannula was inserted into the bile duct proximal to this ligature. Both catheters for selective collection of pancreatic juice and bile were routed subcutaneously and exteriorized at the nape of the neck. Postoperatively, animals were fixed in a sling of adhesive tape attached to an overhead wire that allowed free movement to food and water. In addition, a catheter was inserted into the jugular vein and infusion of saline was started (1 mL/h). Postoperatively, animals were allowed to recover for 20 h. All in vivo experiments were performed on conscious animals. After an overnight fast five rats were fed, by an orogastric tube, one single dose of camostat mesilate (100 mg/kg body wt). In three rats, camostat