Brief Articles

Effects of contrast media on the hepato-pancreato-biliary system

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Received: June 16, 2009 Revised: August 4, 2009 Accepted: August 11, 2009 Published online: October 14, 2009

Abstract

AIM: To determine the effects of high osmolarity contrast media (HOCM) and iso-osmolar contrast media (CM) application, with or without pressure, on hepato-pancreato-biliary (HPB) system.

METHODS: Sixty rats were divided into six equal groups as follows: Group 1: (0.9% NaCl, control), Group 2: (diatrizoate meglumine Na, ionic HOCM, Urographin®), Group 3: (iodixanol, iso-osmolar non-ionic CM, Visipaque®); each of which was applied without pressure, whereas the animals of the remaining three groups (1p, 2p, 3p) were subjected to the same CM with pressure. We performed a duodenal puncture and introduced a catheter into the ampulla. After the catheterization, 0.2 mL CM or 0.9% NaCl was injected with or without pressure. Blood samples were taken for biochemical evaluations. The histopathological examinations of liver, common bile duct, and pancreas were performed.

RESULTS: There were no significant differences between the six groups for blood amylase, alanine aminotransferases, aspartate aminotransferases, bilirubin levels (P > 0.05). Alkaline phosphatase and γ glutamyl transaminase levels were higher (P < 0.05) in the Urographin® groups (2, 2p) than the Visipaque® groups (3, 3p), or control groups (1, 1p). Hepatocyte necrosis, portal area inflammation, and Kupffer’s cell hyperplasia were higher (P < 0.05) in the study groups than the control group. However, there were no significant differences (P > 0.05) between HOCM (2, 2p) and iso-osmolar CM (3, 3p) groups. Bile duct proliferation and regeneration in the Urographin® groups (2, 2p) were significantly higher (P < 0.05) than the Visipaque® groups (3, 3p) or the control groups (1, 1p). Although CM caused minor damage to the pancreas, there were no statistically significant differences (P > 0.05) between the groups. Application of the CM with pressure did not cause additional damage to the HPB system.

CONCLUSION: Iso-osmolar, non-ionic CM could be more reliable than the ionic HOCM, whereas the application of pressure during the CM application had no effect on the HPB system.

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Key words: Contrast media; Liver; Pancreas; Biliary tract; Pressure

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INTRODUCTION

Contrast media (CM) are commonly used in diagnostic imaging methods such as, computerized tomography, magnetic resonance, angiography, cardiac catheterization alone, and imaging of the hepato-pancreato-biliary (HPB) system using endoscopic retrograde cholangiopancreatography (ERCP), percutan transhepatic cholangiography, and intra- and post-operative cholangiography[1]. ERCP is both a diagnostic and therapeutic procedure that has been used for 35 years. Complications of diagnostic ERCP include acute pancreatitis, cholangitis, and cholecystitis[2-4]. Pancreatitis is a major cause of
the morbidity and the mortality related to ERCP. Hyperamylasemia (biochemical pancreatitis) and clinical pancreatitis are seen 20%-70% and 1.8%-6.4% of cases, respectively. It is caused by technical reasons such as the type of CM, frequency of application, fast and pressured injection of the CM, trauma of the sphincterotomy, and the type of diathermy. It is also affected by previous history of pancreatitis, the degree of experience of the endoscopist, and the amount of the injection. Intra- and extra-hepatic bile ducts, along with the pancreatic duct, are imaged during ERCP. Acute cholangitis is another serious complication of ERCP. Most studies on the adverse effects of CM used in ERCP have focused primarily on post-ERCP pancreatitis (PEP). However, the biliary epithelial cells are also exposed to CM during ERCP. Inflammation of the biliary tree, including acute cholangitis and cholecystitis, is another important complication of diagnostic ERCP.

CM can be classified in two groups depending on their ionic properties (ionic or non-ionic) and three types according to their osmolarity (high, low or iso-osmolar). The effect of a CM on image quality during ERCP depends on its density, viscosity, and osmolarity. The image quality appears to be similar when comparing high osmolarity contrast media (HOCM) and low osmolarity contrast media (LOCM). The osmolarity and the ionic nature of the CM are believed to be the major factors responsible for the adverse reactions. Systemic adverse reactions of CM used in ERCP could be characterized as idiosyncratic (anaphylactic; nasal congestion, laryngeal edema, and bronchospasm) or non-iodosyncratic (dose-dependent; renal tubular damage, vascular damage, cardiac depression, and arrhythmia). The prevalence of CM reactions is lower with LOCM (1%-3%) than with HOCM (5%-12%). Fatal reactions are rarely seen, and there is no difference in mortality rates between the two types. An ideal contrast agent must be water soluble, biologically inert, of low viscosity, and should be thermally and chemically stable. It must also have lower or the same osmolarity as human serum, be selectively excreted (via the kidney), and be safe and low cost.

The osmolarity of CM has been implicated as a contributing factor for the development of PEP. However, results of clinical trials are conflicting. One randomized crossover study and four randomized control trials have suggested a benefit from LOCM, while others have not. Animal studies examining pancreatic duct epithelial damage due to CM have also been conflicting. In cats, Bub et al. demonstrated morphologic changes in the pancreatic duct epithelium shortly after injection with CM. Less damage was noted after injection with LOCM. However, Säari et al. demonstrated less acinar destruction with HOCM in pigs. Pfau et al. noted that there were no differences between HOCM and LOCM on pancreatic histology in a canine model.

Damage is caused by technical reasons, such as the type of CM, frequency of application, and the fast and pressured injection of the CM. Hacihametoglu et al. evaluated how intraductal pressure and the use of a contrast agent affect the development of pancreatitis after ERCP. The results of their study suggested a contrast agent should be administered under low pressure when it is needed.

In the present study, the effects of diatrizoate meglumine Na (ionic HOCM, Urografin®) and ioxaglate (iso-osmolar, non-ionic CM, Visipaque®) application with or without pressure on the HPB system were determined.

MATERIALS AND METHODS

Ethics

This experimental study was performed in accordance with the guidelines for the care and use of laboratory animals established by the Ethics Committee of the Cumhuriyet University.

Animal studies

Sixty, three-month-old wistar male rats weighing 250 ± 50 g were used in the present study. The randomly selected animals were supplied by the Animal house of the Faculty of Medicine, Cumhuriyet University. Rats were randomly divided into six equal groups: Group 1: (control, 0.9% NaCl), Group 2: (diatrizoate meglumine Na, Urografin®, ionic HOCM), Group 3: (ioxaglate, Visipaque®, iso-osmolar, non-ionic CM); CMs were used without pressure. The same CMs were applied with pressure in the remaining three groups (1p, 2p, 3p). Rats were anesthetized by an intramuscular injection of ketamine HCl 40 mg/kg body weight (Ketalar: Parke-Davis Eczacıbaşı, Istanbul, Turkey) and xylazin 5 mg/kg body weight (Rompum: Bayer Leverkusen, Germany). All animals were allowed to breathe spontaneously during the experiments. After the abdomen was shaved and cleaned with povidone iodine, a 2 cm midline laparotomy was carried out, and the intestines were covered with sterile gauze pads soaked with isotonic saline at 37°C to minimize evaporation from the tissue. Body temperature was maintained between 36 and 38°C using a heating lamp. In addition, 5 mL Ringer's lactate solution was given subcutaneously to prevent dehydration of the animals during the experimental period. After making a midline abdominal incision, we performed a duodenal puncture by a sharp pointed lancet. We introduced a catheter (0.7 mm diameter) into the ampulla. After catheterization, 0.2 mL CM or 0.9% NaCl was injected with or without pressure. The catheter was then withdrawn. The duodenal puncture was closed by only one suture with an 8-0 polypropylene (prolene). There were no operative and post-operative mortalities. On the second day, blood samples were taken for biochemical assays, including blood amylases, alanine aminotransferases (ALT), aspartate aminotransferases (AST), bilirubin levels, alkaline phosphatase (ALP), and γ glutamyl transaminase (GGT). Animals were kept in separate cages for 15 d, during that time they were fed with rat chow ad libitum and tap water, and kept at room temperature (18-20°C). Fifteen days later, all rats were evaluated for biochemical and histological parameters.
Table 1  Histopathological changes in the liver of rats, extrahepatic biliary ducts, and pancreas

<table>
<thead>
<tr>
<th>Histopathologic changes</th>
<th>Group</th>
<th>1</th>
<th>1p</th>
<th>2</th>
<th>2p</th>
<th>3</th>
<th>3p</th>
<th>P value</th>
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<tr>
<td>Liver of rats</td>
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<tr>
<td>Portal area inflammation</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Bile duct inflammation</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Periductal fibrosis</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Bile duct proliferation</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Hepatocyte necrosis</td>
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<td>0</td>
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<td>Kupffer’s cell hyperplasia</td>
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<td>10</td>
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<tr>
<td>Regeneration findings</td>
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<td>10</td>
<td>8</td>
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<tr>
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<td>Extrahepatic biliary ducts</td>
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<tr>
<td>Inflammation</td>
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<td>2</td>
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<td>3</td>
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<td>0</td>
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<tr>
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<tr>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td>&gt; 0.05</td>
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Numbers indicate the number of the animals in which histopathological changes have occurred; *Indicates the statistical significance.

Histopathological evaluation

Tissue sections from each block were stained with hematoxylin/eosin for histopathological evaluation. We performed histopathological examination of the liver to assess the following: (1) lesions of the lining of the portal and centrilobular areas; (2) lesions of the hepatocytes (focal necrosis, regeneration); (3) biliary duct proliferations; (4) Kupffer’s cell hyperplasia; (5) periductal fibrosis; (6) sinusoidal lesions (distention, fibrosis); (7) parenchymal necrosis; and (8) biliary duct inflammation.

Histopathological examination of the common bile duct was performed in order to assess inflammation, fibroblastic proliferation, and necrosis. We examined the pancreas specimens histopathologically in order to assess inflammation, hemorrhage, and necrosis. The histopathological alterations were evaluated by one pathologist who was blinded as to which group the specimen belonged.

Statistical analysis

All data were analyzed using Kruskal-Wallis variance analysis, and Mann-Whitney U test. The SPSS computer program software (version 9.0; SAS Institute, Cary, NC, USA) was used. A value of $P < 0.05$ was accepted as the significance level.

RESULTS

Biochemical evaluations

There were no significant differences ($P > 0.05$) between the six groups for blood amylase, ALT, AST, bilirubin levels. ALP and GGT levels were higher ($P < 0.05$) in the Urographin® groups (2, 2p) than in the Visipaque® groups (3, 3p), or the control groups (1, 1p). There were no significant differences ($P > 0.05$) between administrations with or without pressure.

Histopathological alterations

All histopathological findings for the liver are given in Table 1. In the liver, there were no significant differences ($P > 0.05$) between the groups for bile duct inflammation, periductal fibrosis, fibrosis, and parenchymal necrosis. Hepatocyte necrosis, portal area inflammation, and Kupffer’s cell hyperplasia were higher ($P < 0.05$) in the study groups than in the control group. However, there were no significant differences ($P > 0.05$) between HOCM [Urographin®, (2, 2p)] and iso-osmolar CM [Visipaque®, (3, 3p)] groups. On the other hand, the above features were not affected by pressure when all the groups were compared. Bile duct proliferation (Figure 1A) and regeneration findings (Figure 1B) in the Urographin® groups (2, 2p) were significantly higher ($P < 0.05$) than the Visipaque® groups (3, 3p), or the control groups (1, 1p). There were no differences ($P > 0.05$) between any groups when CM applications were done with or without pressure (Table 1). Histopathological findings of the pancreas are given in Table 1. Necrosis of the EBT was not seen in any of the groups. Inflammation of EBT was similar in each of the groups. Fibroblastic proliferation in the EBT for the Urographin® groups (2, 2p) were significantly higher ($P < 0.05$) than in the Visipaque® groups (3, 3p), or the control groups (1, 1p). There were no significant differences ($P > 0.05$) between administrations with or without pressure (Table 1).

Histopathological findings of the pancreas were given in Table 1. Necrosis and hemorrhage of the pancreas were done with or without pressure.
were not seen in any of the groups. There were no significant differences ($P > 0.05$) between the groups for inflammation of the pancreas (Table 1).

**DISCUSSION**

The most feared ERCP complication is pancreatitis\[2-6,36\]. It results in morbidity and occasional mortality. Osmolarity of the CM has been suggested to be a risk factor in the development of PEP. There are controversial data in current literature\[37\]. O’Connor et al\[23\] noted that there was no difference in median increments of serum amylase at 6 h after ERCP, but there was a significant difference at 18 h after ERCP in the LOCM (iopamidol) group compared to the HOCM (meglumine diatrizoate) group. No patient, however, developed clinical pancreatitis. Banerjee et al\[27\] determined a significant difference between the abilities of HOCM and LOCM to cause pancreatitis. Their results proved that the incidence of pancreatitis is higher when HO CM is used\[23\]. Barkin et al\[10\] determined the effects of LOCM (iohexol and ioxaglate) and HOCM (meglumine diatrizoate) agents in a prospective, double-blind, randomized study. The clinical symptoms of pancreatitis were lower in patients who received non-ionic LOCM than in those who received ionic HOCM\[38\]. George et al\[10\] determined the incidence of PEP associated with HOCM and LOCM in their meta-analytical study. Clinical pancreatitis was evidenced by both elevation of pancreatic enzymes and pain. The results of their study indicated that there was no significant difference between HOCM and LOCM with respect to clinical pancreatitis\[11\]. Although CM caused minimal adverse effects on the pancreatic tissue, there were no differences between the groups in the present study.

Bub et al\[32\] demonstrated morphologic changes in the pancreatic duct epithelium shortly after injection with CM in cats. Less damage was noted after injection with LOCM. Pfau et al\[34\] noted that there were no differences between HOCM and LOCM on pancreatic histology in a canine model. Saari et al\[35\] performed experimental pancreatography on 25 piglets using three CM [diatrizoate meglumine Na (ionic HOCM), meglumine ioxaglate (ionic LOCM), and iohexol (non-ionic LOCM)]. They also injected the CM very slowly in order to avoid elevation of intraductal pressure and used a narrow cannula to enable free escape of pancreatic fluid and CM from the ductal system during injection, thus prevented overfilling. Minimal acinar destruction was seen on histological examination in all cases. This study showed that diatrizoate meglumine Na was rapidly emptying compared to the other CM; therefore the changes were least when diatrizoate was used. The emptying of CM from the ducts was significant. Saari et al\[35\] noted that rapid emptying might be an advantage in clinical ERCP. Haciahmetoglu et al\[36\] evaluated how intraductal pressure and contrast agent affect the development of pancreatitis after ERCP. The results of their study suggested that the main mechanism for preventing pancreatitis after ERCP is to minimize trauma to the pancreatic canal, to cannulate the pancreas only when it is necessary, and to give contrast agent under low pressure when it is needed. In the present study, all of the CM were applied with and without pressure, but no difference ($P > 0.05$) was observed between them.

Mäkelä et al\[37\] determined no difference in the incidence of hyperamylasemia between diatrizoate meglumine (ionic HO CM) and iohexol (non-ionic LOCM) groups. The authors concluded that acute hyperamylasemia after ERCP was a complication of relatively minor importance, unlikely to be reduced by the use of LOCM\[37\]. In the present study, there was no difference between the groups for the serum amylase measures.

Biliary epithelial cells are also exposed to CM after the ERCP procedure. Ju et al\[37\] performed a study to compare the cytotoxicity with gallbladder epithelial cells of ionic and non-ionic CM. They tested HOCM and LOCM for their effects on monolayer cell cultures of dog gallbladder epithelial cells. According to their results, HOCM were more cytotoxic than LOCM in gallbladder epithelial cells. In the present study, we observed that ionic HOCM were more destructive for the biliary tracts. In the literature, there are numerous studies on the effects of CM on pancreas, but fewer studies on the biliary tract\[37\] and liver\[38\]. In our study, we also evaluated biliary tract and liver. The findings revealed that HOCM...
were more destructive than the iso-osmolar CM on the biliary tract and liver. These histopathological findings were also confirmed biochemically in the HOCM groups (group 2, 2p) by elevated ALP and GGT levels.

In conclusion, the findings of the present study have pointed out that iso-osmolar non-ionic CM could be more reliable than the ionic HOCM during the application of ERCP and diagnostic methods used for the imaging of the extra-hepatic biliary tracts. On the other hand, CM application with pressure might not cause additional damage to the HPB system.

COMMENTS

Background

Contrast media (CM) are commonly used in diagnostic imaging methods in visualizing the hepato-pancreato-biliary (HPB) system using Endoscopic retrograde cholangio pancreatography (ERP), percutan transhepatic cholangiography, and intra- and post-operative cholangiography. Complications of diagnostic ERCP include acute pancreatitis, cholangitis, and cholecystitis.

Research frontiers

There are no experimental studies on effects of the iso-osmolar, non-ionic CM on the HPB system. Most studies on the adverse effects of CM used in ERCP have focused primarily on post-ERP pancreatitis (PEP). However, the biliary epithelial cells are also exposed to CM during ERCP. Inflammation of the biliary tree, including acute cholangitis and cholecystitis, is another important complication of diagnostic ERCP. Therefore, the present study involved in the effects of high osmolarity contrast media (HOCM) and iso-osmolar CM on HPB system histopathologically and biochemically. In addition, the present study has also studied the effects of pressure during the injection of CM into the HPB system.

Innovations and breakthroughs

Although osmolality of the CM has been suggested to be a risk factor in the development of PEP, there are controversial data in current literature. While there are several studies comparing the effects of low osmolality contrast media and HOCM in the development of PEP, there are no studies on the comparison of the effects of non-ionic, iso-osmolar CM.

Applications

Findings of the present study have pointed out that iso-osmolar non-ionic CM could be more reliable than the ionic HOCM during the application of ERCP and diagnostic methods used for the imaging of the HPB system. On the other hand, CM application with pressure might not cause additional damage to the HPB system.

Peer review

The paper on the effect of the osmolality of CM on the hepatobiliary tract is an interesting topic.

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