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Acute tissue response of biliary and gastrointestinal system to methyl - tertiary - butyl ether infusion into the gallbladder of rabbits

Safra keselerine metil - tert - bütil - eter infüzyonu yapılan tavşanlarda, biliyer ve gastrointestinal sistemin akut doku yanıtı

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ÖZET: *Son yıllarda safra taşlarının tedavisinde, yeni teknikler kullanılmaktadır. Bunlardan birisi olan, Metil-Tert-Bütil-Eter (MTBE) ile safra taşı eritilmesi de, halen bazı merkezlerde uygulanmaktadır.*

Bu çalışmada biz, güçlü bir kolesterol çözücü ajan olan MTBE'nin biliyer ve gastrointestinal sistemdeki akut doku cevabını ortaya koymayı amaçladık. Çalışmaya 8 Yeni Zelanda tipi tavşan alındı. Tavşanların safra kesesine 5 French biliyer kateter, cerrahi olarak yerleştirildi. Laparotomiden hemen sonra, 6 saat süresince, 0.5-0.7 ml. MTBE solusyonu, manuel olarak safra keselerine uygulandı. Kontrol grubuna ise kateter yolu ile, serum fizyolojik verildi. Uygulamadan 6 saat sonra, hayvanlar sakrifiye edildi.

Işık mikroskobunda, MTBE uygulanan tavşanların safra keselerinde ve safra yollarında, değişik derecede, nekroz, propriada hemoraji ve ödem gözlendi. Serum fizyolojik uygulanan kontrol grubunun safra keselerinde ise küçük kanama odakları ve nekroz izlendi. Kontrol grubu ile mukayese edildiğinde, MTBE uygulanan tavşanlarda, nekroz oldukça ciddi boyutlarda idi.

Çalışmamızda, MTBE uygulamasının, ciddi akut yan etkileri gösterildi. Bu hayvan çalışmasının sonuçları, her ne kadar direkt olarak insanlara yansıtılmasa da, safra taşları tedavisinde MTBE'nin dikkatle kullanılması gerekliliğini ortaya koymaktadır ve eğer uygulanacaksa, bu hastalar sıkı kontrollerle yakından takip edilmelidir.

Anahtar Kelimeler : **Metil - tert - bütil - eter, safra taşı**

SUMMARY: *New approaches have been recently introduced in treatment of gallstones. Gallstone dissolution with methyl tertiary butyl ether, one of these new techniques, has been used by some authors.*

Eight New Zealand type rabbits were studied. 5 French Biliary drainage catheter was surgically sutured into the gallbladder of rabbits. Immediately after laparatomy, methyl tertiary butyl ether was manually instilled into the gallbladder in aliquots of 0.5-0.7ml. for 6 hours period. Saline solution was instilled into the gallbladder of control animal through the catheter. Animals were sacrificed after 6 hours.

On light microscopy, rabbits treated with methyl tertiary butyl ether had different degrees of gallbladder and common bile duct necrosis, proprial hemorrhage and edema. Control animals receiving saline solution showed small hemorrhages and necrosis in the gallbladder. The severity of necrosis was extremely high in the methyl tertiary butyl ether treated rabbits as compared with the controls.

Methyl tertiary butyl ether application produced severe acute side effects in our rabbit study. Although the results of this animal study can not be directly transferred to humans, the data suggest that methyl tertiary butyl ether should be used in gallstone therapy with caution and a meticulous follow-up is necessary in the treated patients.

Key words : **Methyl - butyl - ether, gallstone**

INTRODUCTION

New non-surgical approaches alternative to standard cholecystectomy have been increasingly more popular in the treatment of gallstones especially in patients who have increased surgical risk.

One of these new techniques, medical dissolution of cholesterol stones was first published by Walker in 1891 (1). Since that time many attempts have been made to provide the safest and most reliable method of treating cholelithiasis by infusion of other solvents. Thistle and Allenís study groups suggested methyl tertiary butyl ether (MTBE) solvent as a new therapeutic approach for dissolution of cholesterol gallstones (2,3). Until now on, even though some adverse effects due to MTBE have been described, tissue response of biliary system, liver and duedonum is not well known.

In this study, we aimed to evaluate the anatomopathologic acute changes due to MTBE in animal models before clinical application.

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MATERIAL AND METHODS

MTBE is an aliphatic ether with an excellent cholesterol-solubilizing capacity, and because of its higher boiling point (55.20 C) it remains liquid at body temperature. After absorption in the gut, a small percentage of MTBE may be metabolized to methanol, formaldehyde, and formic acid and furthermore to tert-buthanol. MTBE, methanol and tert-buthanol in sufficient concentrations are potentially toxic compounds and may be stored in tissues (2).

In our study, eight New Zealand type rabbits (two controls, six experiments) were used. Average body weight was 2.35 kg. (range: 2.0-2.8kg.). Animals were anesthetized by ketamine and laparatomy was performed. The gallbladder was punctured and 5 French catheter was introduced. During operation, bile volumes in the gallbladders of the rabbits were meosured. Soon after laparatomy, MTBE of 0.5-0.7ml. was installed into their gallbladders through catheter for six hours. In every thirty minute, the solutions were removed and refilled. In control subjects, saline solution of the same amount was installed for the same period.

To prevent fluid loss, a buffered Ringer's solution was infused intravenously. To prevent hyperhydration, haematocrit count was obtained every hour. For controlling the level of anesthesia, animals were monitorized by ECG. Body temperature was kept constant at 38 C.

Treated rabbits and controls were sacrificed after six hours from application.

For histological examinations the gallbladder, common bile duct, duodenum, liver, pancreas, lung and kidney tissue samples were fixed in buffered 10% neutral formalin solution, and paraffin sections were cut at 6 micron and stained with hematoxyline-eosine.

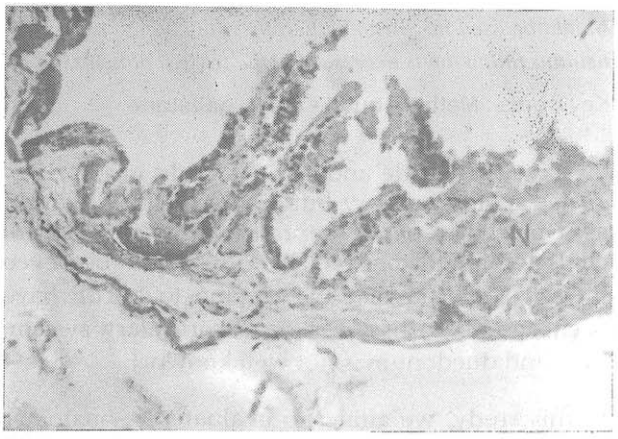

Figure 1: *Case 2, Degenerative epithelial changes and necrotic foci (N) of the galibladder mucosa (HxE X 110).*

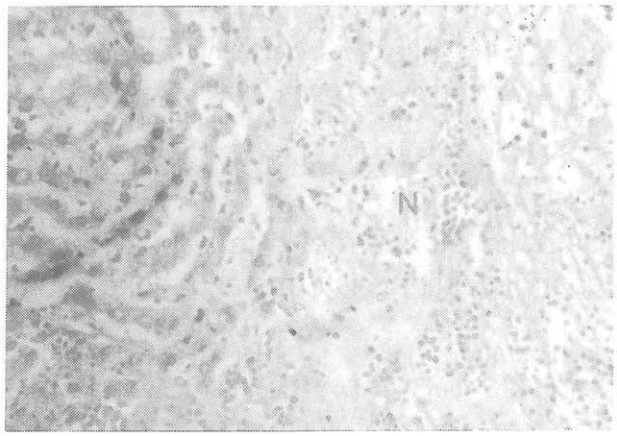

Figure 2: *Case 6, Necrosis (N) of the liver parenchyma (HxE X 300).*

Figure 3: *Control rabbit. A small area of necrosis (N) of the gallbladder (HxE X 110).*

RESULTS

Grossly, small areas of necrosis and hemorrhage were seen on the gallbladder mucosae of treated rabbits. On light microscopy the gallbladder and common bile duct showed total necrosis in two animals. In other four, necrotic foci were small and multifocal in distribution (Figure 1). Proprial hyperemia, hemorrhage and edema were prominent in all cases. In two rabbits, slight inflammation was

Table 1:*Histological Changes of the MTBE Treated Rabbits (N = 6)*

	Rabbits					
Histological Changes	1	2	3	4	5	6
Necrosis						
Diffuse					+	+
Multifocal	+	+	+	+		
Proprial Hyperemie, hemmorhage and edema	+	+	+	+	+	+
Slight Inflammation	+		+			
Common Bile Duct						
Necrosis						
Diffuse					+	+
Multifocal	+	+	+	+		
Liver						
Passive hyperemie, hemmorhage and small area of necrosis			+	+	+	+

observed in the lamina propria. Surrounding liver tissue showed passive hyperemia, hemmorrhage and small areas of necrosis in four cases (Figure 2). There was no histological change of other visceral organs except slight duodenal hyperemia. Histological changes of MTBE-treated rabbits are summarized in Table 1.

Control rabbits received saline solution showed small hemorrages and necrosis in the gallbladder (Figure 3). The severity of necrosis was extremely high in the MTBE-treated rabbits compared with the controls.

DISCUSSION

There are few reports about tissue response of biliary and digestive system after gallstone dissolution by MTBE. Van Sonnenberg et al. noted successful dissolution of gallstones without tissue response in one patient (4). Di Padova et al. described a slight duodenitis in one of three patients (5). Vogelzang and Nemcek reported a gangrenous cholecytitis in two patients (6). Leuschner et al. reported chronic cholecytitis in six patients (7). This was considered as an effect of stones rather than MTBE administration.

The effect of MTBE on animal tissues was experimentally investigated in dogs, pigs and rabbits. Allen et al., after MTBE application in six dogs, observed mild nonspesific inflammatory changes of gallbladder mucosa (2). Peine et al., described same-day sequential ESWL fragmentation and MTBE dissolution of gallstones in dogs (8). The results demonstrated that although ESWL causes moderate trauma to the gallbladder, this does not result in histological evidence of mucosal disruption.

Mc Gahan et al., demonstrated that surgically implanted gallstones in swine can be dissolved with 3 to 7 days of continuous MTBE infusion. They reported mild superficial ulcerations of the gallbladder in a series of six pigs after MTBE application (9).

Adam et al., evaluated the tissue response of the biliary and digestive system after MTBE application in 32 rabbits. All rabbits had different degrees of gallbladder, common bile duct and intrahepatic bile duct necrosis. Control animals had only small areas of necrosis in the biliary system.

One results are very similar to those of Adam et al. The gallbladder and common bile duct necrosis developed in all rabbits, being diffuse in two and multifocal in four. Slight vascular and inflammatory changes were also seen. Effects of MTBE and catheter application might be responsible for these mucosal necroses.

Surrounding liver tissue response i.e. passive hyperemia, hemorrhage and small areas of necrosis could have resulted from leakage of bile or MTBE from the catheter.

MTBE application produced severe acute side effects in our rabbit study. Although the results of this animal study can not be directly transferred to humans, the data suggest that MTBE should be used gallstone therapy with caution; if it will be used, a well-controlled follow-up of these patients is necessary.

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