

*Liver and biliary***Cholelithiasis – in vivo stone dissolution using methyl tertiary butyl ether (MTBE)**

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SUMMARY We report a series of 10 elderly patients with large bile duct calculi refractory to standard endoscopic extraction techniques who were treated by gall stone dissolution using methyl tertiary butyl ether (MTBE) instilled through a nasobiliary catheter. In eight patients complete bile duct clearance was achieved after an average of eight hours MTBE instillation. In two patients gall stone size did not change. Both underwent operative gall stone removal and subsequent stone analysis showed low cholesterol content, which is unlikely to respond to MTBE. Apart from occasional transient nausea and drowsiness, no adverse reactions were noted. Methyl tertiary butyl ether appears to be a powerful *in vivo* gall stone dissolution agent which, from preliminary studies, is not associated with serious toxicity.

Endoscopic sphincterotomy (ES) has revolutionised the management of gall stones in the extrahepatic bile duct. The present success rate of bile duct stone clearance using endoscopic techniques based on ES varies from 77% to 90%.¹⁻³ The most common reason for failure to achieve bile duct clearance is related to stone size and is encountered when large calculi cannot be delivered through a complete sphincterotomy. Mechanical and ultrasound lithotripsy have not yet been fully developed for use in the bile duct⁴ and therefore in most centres surgery is the only treatment option remaining after failed endoscopic stone extraction. Cholelithotomy in the elderly, however, may carry a high morbidity and mortality,⁵ a fact which may well have been the main reason for referring a patient for endoscopic management in the first place. In addition, surgical bile duct exploration does not always result in complete clearance of gall stones.²

Gall stone dissolution has been considered a potential solution to this problem but despite nearly 100 years of research neither the ideal chemical nor delivery route has been found. Many of the dis-

solution agents tested had unsatisfactory physical properties and a high incidence of side effects was noted during therapy.⁶ Until recently the most effective agent available for this use was the mono-glyceride mono-octanoin. In 1986 Palmer and Hoffman⁷ reviewed the published world experience of 343 cases of mono-octanoin dissolution therapy and showed a disappointing success rate of 54% with a 67% incidence of side effects, 5% of which were life threatening. In 1985 Allan *et al*⁸ reported the first successful cases of *in vivo* dissolution of gall stones in the gall bladder and bile ducts using methyl tertiary butyl ether (MTBE) administered either directly into the gall bladder *via* a percutaneous transhepatic catheter, or into the bile duct *via* an nasobiliary catheter (NBC). We have recently reported a case⁹ in which MTBE, administered through a nasobiliary catheter after endoscopic sphincterotomy, resulted in the fragmentation of large cholesterol gall stones in the common bile duct allowing subsequent duct clearance of debris using a balloon catheter. We have continued to use MTBE in this context and now report our experience with our first 10 patients.

Methods**PATIENTS**

During the 15 month period between January 1986

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and March 1987, 280 patients were referred to one consultant (WRM) at the Western Infirmary, Glasgow, for ERCP. One hundred and four of these patients were shown to have choledocholithiasis by endoscopic cholangiography using an Olympus JFIT duodenoscope. In 90 patients (86.5%) immediate or delayed bile duct stone clearance was achieved after endoscopic sphincterotomy using an Olympus papillotome knife and an Olympus PSD diathermy unit. Endoscopic sphincterotomy failed in four patients (3.8%). In 10 patients (9.6%) gall stone retrieval failed after a sphincterotomy judged to be close to the maximum length compatible with safety and attempts at stone extraction using both a balloon catheter (Diagmed Limited) and a metal basket (Olympus FG 18/12). At screening cholangiography stones (1–12 per patient) were seen to be large in all 10 cases (>15 mm diameter) and stone impaction within the sphincterotomy site occurred in two patients. In both cases stones were released into the bile duct after further basket manipulation. Once failure of stone extraction was recognised a polyethylene nasobiliary catheter (Wilson-Cook Med Inc) was placed into the bile duct through the duodenoscope. The NBC was rerouted through the nose and connected to a bile bag to allow free drainage of bile and subsequent sampling for bacteriology.

The 10 patients thus selected for MTBE dissolution therapy consisted of eight women and two men with a mean age of 74 (range 65–85 years). Six patients had undergone cholecystectomy between six months and 20 years previously, while all the remaining four patients had ultrasound evidence of cholelithiasis. The patients' main presenting signs or symptoms were as follows: obstructive jaundice (three), cholangitis (three), biliary pain (two), pancreatitis (one) and abnormal liver function tests (one).

ADMINISTRATION OF MTBE

A check NBC cholangiogram was carried out 24 hours after endoscopic sphincterotomy and NBC insertion to ensure the catheter still lay within the bile duct. The NBC was carefully manipulated to position the terminal pigtail round the gall stone nearest the liver. The patient was returned to the ward and placed supine in bed. The NBC was aspirated to dryness through a three way tap and after this an aliquot of MTBE (2–5 ml: British Drug Houses) was injected down the NBC which was then closed. After 30 minutes the NBC was aspirated to remove bile, residual MTBE and any debris which had accumulated in the bile duct and a further aliquot of MTBE injected. This whole procedure was repeated until four aliquots of MTBE (8–20 ml in total) had been instilled over a two hour period. The amount of

MTBE instilled in each aliquot was determined by factors such as the number of stones to be treated, the proximity of the NBC to the stones, the bile duct size and the patient's reaction to the chemical. The pulse, blood pressure and level of consciousness were monitored during the periods of MTBE administration. Ether could be easily detected from the patient's breath within minutes of the first administration of MTBE and smoking was not allowed within the vicinity.

An NBC cholangiogram was carried out approximately 24 hours after each treatment session and these cholangiograms were used to check the position of the NBC and to assess the effect of the MTBE on the gall stones. The development of a 'moth eaten' appearance of the gall stones was common and indicated dissolution activity. This radiological appearance correlated well with the finding of stone fragments in the NBC aspirate fluid during MTBE treatment. Methyl tertiary butyl ether treatment sessions were repeated at 48 hour intervals until either spontaneous stone passage occurred or fragmentation likely to allow endoscopic extraction was noted. Methyl tertiary butyl ether treatment was considered to have failed when the NBC aspirate contained no debris over two treatment sessions or when two consecutive cholangiograms failed to show radiological evidence of stone dissolution.

Results

Spontaneous bile duct clearance confirmed by nasobiliary cholangiography was seen in three patients after three, three and four MTBE treatment sessions respectively. Partial gall stone dissolution with fragmentation was seen in five patients after an average of four treatment sessions. One patient subsequently passed their stone fragments spontaneously while four required endoscopic extraction. In these four patients soft debris was noted in the bile duct at ERC and duct clearance did not prove difficult.

Methyl tertiary butyl ether dissolution therapy failed in two patients, both proceeding to successful surgical removal of their gall stones. Chemical analysis of these gall stones revealed a low cholesterol content of 40% and 35% respectively.

Methyl tertiary butyl ether administration through an NBC resulted in nausea and slight drowsiness in one patient and transient hypertension in another. Minor rises in the liver transaminases were occasionally noted at the end of an MTBE treatment session. These changes returned to normal after 24 hours and the general trend was of an improvement in overall liver function related to NBC drainage of bile.

Discussion

Methyl tertiary butyl ether is a stable colourless aliphatic ether having a specific gravity of 0.74. Its pharmacokinetics are similar to diethyl ether in many respects in that it is inflammable, narcotic in high doses and a powerful solvent of cholesterol. Unlike diethyl ether which vaporises at body temperature (boiling point=34.5°C), MTBE remains a liquid at body temperature (boiling point=53°C) and is therefore suited for use in the biliary tree. *In vitro*, cholesterol gall stones dissolve with remarkable rapidity in MTBE.¹⁰ Dissolution is enhanced by the absence of bile and close contact between the gall stones and the ether.¹¹ Close contact between MTBE and gall stones in the bile duct can be a problem in clinical practice. Methyl tertiary butyl ether floats on bile because of its low specific gravity and the natural tendency is therefore for the ether and gall stones to separate. We regard the positioning of the pigtail portion of the NBC as crucial. Radiological visualisation of the ether is possible by mixing it with a lipid soluble radio opaque contrast medium.¹² This allows accurate adjustment of the position of both the NBC and the patient to maximise contact between ether and stones. Bile duct aspiration *via* the NBC before MTBE administration also facilitates contact and should not be omitted.

Methyl tertiary butyl ether is a powerful organic solvent and must be handled with care. Any material that may come in contact with the ether during its administration should first be tested *in vitro* to ensure that it is resistant to dissolution. Methyl tertiary butyl ether will rapidly dissolve surgical T-tubes placed in the extrahepatic bile duct and on no account should the ether be administered *via* this route. Polyethylene and related substances are resistant to MTBE dissolution and should generally be safe when used with this chemical.

Eight of 10 patients in this series achieved a successful conclusion to their dissolution therapy with MTBE after an average exposure of only eight hours. These results show rapid *in vivo* gall stone dissolution and are superior to those obtained with any other cholesterol solvent administered in this way.¹³ Complete gall stone dissolution is not necessary when MTBE is used in this context. Provided that a full length endoscopic sphincterotomy is carried out partial gall stone dissolution or fragmentation is all that is required to allow spontaneous or instrumental stone passage into the duodenum. We

believe that likely treatment failure with MTBE can be detected within 72 hours of first placing the NBC, thus allowing other treatment options to be considered without undue delay. We have used this ether in a frail group of elderly patients and have been encouraged by the lack of side effects encountered. We have no doubt that this technique can have a place in the management of selected patients with both cholelithiasis and cholelithiasis but would caution against the indiscriminate use of an inflammable and potentially toxic chemical such as MTBE.

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