GALLSTONE LITHOTRIPSY

A REPORT

BY THE

NATIONAL HEALTH TECHNOLOGY ADVISORY PANEL

DECEMBER 1988

AUSTRALIAN INSTITUTE OF HEALTH

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GALLSTONE LITHOTRIPSY

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GALLSTONE LITHOTRIPSY

EXECUTIVE SUMMARY

- Extracorporeal shock wave lithotripsy (ESWL) is now being applied to treatment of stones in the **gallbladder** and **bile duct**. At least five types of machine designed for lithotripsy of stones in the biliary tract have become available.

- ESWL of **gallbladder** stones is followed by a period of oral bile acid therapy (ranging from 8 to 30 months) to achieve clearance of stone fragments.

- Bile acid therapy is not used with ESWL of **bile duct** stones. Fragments pass spontaneously, especially if endoscopic sphincterotomy has been performed, or are removed endoscopically.

- As yet only limited data are available from clinical trials of gallstone ESWL with bile acid therapy. Further information is needed before firm conclusions can be established on success rates, complications, duration of bile acid therapy, rate of recurrence of stones, and costs.

- In comparison with surgical removal of the gallbladder, gallstone lithotripsy has the advantages that
  - open surgery and general anaesthesia are avoided
  - the recovery period is reduced
  - morbidity and mortality may be lower.

- It has the disadvantages that
  - it does not provide a permanent cure and recurrence of stones is likely
  - it can only be applied to a limited proportion of patients eg those with three stones or fewer
  - it is part of a prolonged treatment regimen.

- The cost of lithotripsy of **gallbladder** stones can fall within a wide range (on a preliminary estimate, $1,900-$8,100 if there is only one ESWL treatment). Major factors affecting costs are the duration and dosage rates required for the bile acid therapy.

- Preliminary estimates suggest that in many cases it would have a cost advantage over cholecystectomy. The advantage would be lost if an extended period of treatment with bile acids were required.

- Estimates based on a model with very preliminary assumptions suggest that compared with cholecystectomy, ESWL of gallbladder stones will have an overall cost advantage for a population of patients unless there is a significant rate of repeat treatment.

- If gallstone lithotripsy is used to treat patients who would not be considered for cholecystectomy, it will be and additional cost to health care.

- The cost of lithotripsy of bile duct stones may fall within the range $2,100-3,300. It would have a cost advantage over surgery but not over endoscopic removal of stones. It may have a useful role in the treatment of stones which cannot be removed endoscopically.

- The routine clinical use of ESWL for gallbladder or bile duct stones in Australia would be premature, at this stage, given the limited data available.

- The Panel considers that this technology should not yet be used in Australia except in the context of a clinical trial with a well designed assessment protocol. No more than one unit would be justified in the trial phase.

- The unit should be sited in a major hospital with expertise in biliary disorders, experience in clinical evaluation, and adequate back-up facilities.

GALLSTONE LITHOTRIPSY

INTRODUCTION

In 1985, the National Health Technology Advisory Panel (NHTAP) issued a report on the use of extra-corporeal shock wave lithotripsy (ESWL) for the treatment of stones in the urinary tract (1). The Panel noted that the scope of the technology would be substantially increased if it could be applied to gallstones. At that time the technology had not been adapted to this application.

In December 1987 the Panel completed an information paper (2) which reported new developments in ESWL including its application to gallbladder and common bile duct stones. Several lithotripters designed for use with stones in the biliary tract were described.

As gallstone lithotripters became available, the Panel saw a need to examine the status, efficacy and cost effectiveness of the technology, its potential impact on Australian health care, and whether its introduction was desirable. This report is intended to provide advice on these questions to health authorities and other interested bodies. It covers ESWL of both gallbladder and bile duct stones.

GALLSTONES AND THEIR EFFECTS

Function of the Gallbladder and Bile Ducts

The gallbladder is essentially a reservoir for bile, the emulsifying agent secreted by the liver to aid in digestion. The gallbladder is linked by the cystic duct to the common bile duct, which conducts bile from the two hepatic ducts to the duodenum, entering it at the papilla of Vater, through a muscular sheath called the sphincter of Oddi. About 30 minutes after ingestion of food, the gallbladder contracts, the sphincter relaxes and bile is emptied through the cystic and common ducts into the duodenum.

Types of Gallstones

Gallstones may be divided into cholesterol stones in which the predominant constituent is cholesterol, and pigment stones, which contain large proportions of calcium bilirubinate, and in which cholesterol is a minor constituent.

In Western countries, 70-80% of gallstones are of the cholesterol type, which are formed from excess cholesterol in the bile (3). They may be pure cholesterol (usually single, large stones with a diameter greater than 2.5 cm), or heterogeneous, resulting from the coalescence of cholesterol around some other material. These heterogeneous stones tend to be smaller, with a diameter of 0.5 to 2.5 cm, and are usually multiple. Cholesterol stones are usually radiolucent (transparent to X-rays), but some containing calcium are radio-opaque.

Pigment stones are of two types. Black pigment stones occur principally in subjects of European extraction and are usually found only in the gallbladder. Brown pigment stones are found both in the gallbladder (particularly in patients of Asian extraction) and in the bile ducts.

Prevalence of Gallstones

It has been suggested that 25% of women and 20% of men in developed countries will have gallstones at some time in their lives (4). On the basis of a study in Framingham, Massachusetts in the 1960s, the prevalence of gallstone cases in the USA has been estimated to be 20 million, with one million new cases discovered each year. Some 500,000 Americans have cholecystectomies (surgical removal of the gallbladder) annually (5). In a study in Italy begun in 1980, in which ultrasound was used for the detection of gallstones, 14% of men and 20% of women between the ages of 54 and 63 years were found to have gallstone disease (6).

If the proportion of cases in Australia is similar to that in the USA, over one million people in this country could have gallstones. However, it cannot be assumed that all western countries will have a similar prevalence of gallstone disease and there is a need for local studies. As discussed later in this report, about 23,000 cholecystectomies are performed annually in Australia.

Effects of Gallstones

Usually patients with gallstones are asymptomatic. While in the past there has been a tendency to regard all gallstones as likely to cause problems, more recent studies suggest that the majority of asymptomatic gallstones remain so (7, 8). Data from a longitudinal study in Italy have shown that up to 18% of asymptomatic cases develop symptoms within 20 years (Toouli, personal communication). The Panel notes that a patient who becomes aware of having gallstones may experience anxiety and psychosomatic symptoms.

Flatulent dyspepsia is often associated with gallstones, but can have a variety of other causes. More seriously, gallstones may cause episodes of severe pain, called biliary colic, which can occur if they move into the cystic duct or become impacted in a pocket of the gallbladder. it may be difficult to establish whether the pain observed has a biliary origin.

Acute inflammation of the gallbladder (acute cholecystitis) is usually related to the presence of gallstones. It can be followed by chronic cholecystitis in which the gallbladder is thickened, fibrosed, and usually infected. Pancreatitis is sometimes induced by gallstones. Gallbladder carcinoma is believed to be associated with the presence of gallstones, but the incidence is generally low. One study found an estimated 20-year cumulative risk of gallbladder cancer in white women with gallstones of 0.5% (9).

Stones found in the common bile duct usually originate from the gallbladder. Only relatively small stones can pass from the gallbladder into the bile ducts, but once there they can enlarge. Occasionally, stones are also found in the hepatic ducts. There may be one or a number of stones in the bile ducts. They can be present for many years without giving rise to symptoms, but commonly they cause acute or intermittent obstruction.

Acute obstruction is usually due to the impaction of a stone at the point where the common bile duct becomes narrower before entering the duodenum. It causes obstructive jaundice, with severe pain and nausea. The symptoms usually last for a few days, after which the stone may pass into the duodenum or swelling subsides, and bile flows freely again. In intermittent obstruction, the blockage is insufficient to cause jaundice, but the ducts are dilated, with thickened walls.

Stones in the common duct are frequently associated with infection in the bile. This can cause the serious complication of cholangitis (inflammation of a bile duct).

DESCRIPTION OF GALLSTONE LITHOTRIPSY

Technology

ESWL is based on the principle that an externally generated shock wave, focused on a hard object within the body, can fragment the object without significant damage to the soft tissues through which the shock wave passes. Several types of lithotripter are being used to treat biliary stones (2). Summary information on current models is given in Table 1.

A lithotripter must incorporate mechanisms for

- generating and focusing shock waves;
- transmitting the wave to the body without disruption;
- locating the stone to be fragmented and aligning it with the shock wave focus; and
- monitoring progress in stone fragmentation.

The first technique developed for shock wave generation was spark discharge. It is still used in second generation Dornier lithotripters, including the MPL-9000 which has been designed for use with both gallstones and kidney stones. Spark discharge is also used in the Technomed Sonolith devices.

Alternatively, shock waves may be generated by piezoelectric systems, as in the Wolf and EDAP units, or electromagnetically as in the Siemens Lithostar.

Since water and body tissues have similar acoustic impedance, water can be used as a medium for the transmission of shock waves from the generator to the body. (Air has a very different impedance value and cannot be used as the medium.)

In the first generation lithotripters, shock waves were transmitted through a water bath in which the patient was suspended. In machines used for gallstone lithotripsy, the water bath has been eliminated; transmission is through a column of water which is either in direct contact with the patient's body, or coupled to the body by means of a membrane and coupling gel.

In kidney stone ESWL, fluoroscopy has generally been used in the past for locating and positioning stones, and monitoring their disintegration. However, it cannot be used in gallstone ESWL since most gallstones are radiolucent. Instead, ultrasound is used. The Dornier MPL-9000 lithotripter incorporates two ultrasound scanners, one on a multi-articulated (robot) arm, the other integrated into the shock wave unit. The stone to be fragmented is located with the scanner on the robot arm. Using geometric information from the robot arm and data from a light pen which marks the position of the stone on a display screen, a computer calculates the position of the stone relative to the shock wave focus. The patient is on a stretcher which can be moved in a number of directions under computer control. The stretcher is positioned to bring the stone into focus. The second ultrasound scanner, in the shock wave generator, is used to provide further control of stone position, and visualise the disintegration process.

In other lithotripters which have been used to treat gallstones somewhat different approaches have been used. In particular, the stone is brought into the shock wave focus by moving the shock wave generator rather than the patient. The Technomed Sonolith has an ultrasound scanner mounted on an articulated arm. In the Wolf Piezolith 2300, two ultrasound scanners are mounted on the piezoelectric dish. The EDAP-LT01 incorporates a hand-held probe as well as a scanner integrated into the shock wave generator.

Most manufacturers of machines designed for gallstone lithotripsy advise that general or epidural anaesthesia is not required.

Associated Treatments

In kidney stone ESWL, the fragments produced by the treatment are usually excreted naturally in the urine. The removal of fragments from the gallbladder is more difficult. There are barriers to excretion in the form of spiral valves in the cystic duct, and the sphincter of Oddi at the entrance of the common bile duct to the duodenum. In addition, the gallbladder may have less contractile ability as a result of disease, and the common bile duct has no peristaltic capability to aid excretion (10).

The Panel understands that in some cases fragments of gallbladder stones are spontaneously excreted after ESWL. However, in most cases chemical treatment is required to dissolve all the fragments. To date, oral bile acid therapy with ursodeoxycholic acid and chenodeoxycholic acid has been used for the dissolution of fragments from lithotripsy of gallbladder stones (10-12). In a sense, ESWL may be seen as a means of facilitating chemical dissolution of gallbladder stones.

Oral bile acids are less effective against stone fragments in the common bile duct. The removal of these may depend on natural excretion, which will occur more readily in patients who have had an endoscopic sphincterotomy, or they may be removed endoscopically.

TABLE 1: GALLSTONE LITHOTRIPTERS

Descriptors	Dornier MPL-9000	Wolf Piezolith 2300	EDAP LT01	Technomed Sonolith 3000	Northgate SD-3	Siemens Lithostar Super
Shock Wave Transducer	Spark discharge	Piezoelectric	Piezoelectric	Spark discharge	Spark discharge	Piezoelectric (for gallstones) plus electro magnetic
Shock Wave Transmission	Water column-membrane-gel	Degassed water in direct contact with patient	Water column-membrane-gel	Degassed water in direct contact with patient	Water column-membrane-gel	Water column-membrane-gel
Stone Visualisation	Dual ultrasound robot arm, shock wave unit	Dual ultrasound in shock wave unit	Ultrasound in shock wave unit, hand-held probe	Ultrasound on articulated arm	Ultrasound on articulated arm	Ultrasound in piezelectric unit plus X-ray
Status	Clinical trials	Clinical trials	Clinical trials	Clinical trials	Experimental (animals)	Clinical trials
Method of Focussing Shock Wave	Movement of patient stretcher	Movement of shock wave unit	Movement of shock wave unit	Movement of shock wave unit	Movement of shockwave unit	Movement of Patient stretcher
Shock Wave Gating	ECG and/or respiratory	None		ECG	ECG	ECG and/or respiratory
Used for Renal Stones ?	Yes	Yes	Yes	Yes	Yes	Yes
Anaesthesia required?	No	No	No	No	Yes	No

Status of the Technology

The Panel has been advised that the Dornier MPL-9000 has been used with more than 2,400 gallstone patients, although to date only limited results have been published. The company has received FDA approval for clinical trials of the MPL-9000 in the USA and these are proceeding at ten sites.

The EDAP LT01, Technomed Sonolith, Siemens Lithostar and Wolf Piezolith machines have all been applied to biliary stones in humans, but as yet the number of patients treated are believed to be quite small. At this stage, although all these lithotripters are commercially available, none of them could be regarded as proven for routine clinical use in biliary applications.

Chenodeoxycholic acid is freely available in Australia, but is not covered under the Pharmaceutical Benefits Scheme. Ursodeoxycholic acid is regarded as an investigational drug, available for use only in adequately designed clinical trials.

EXISTING FORMS OF TREATMENT OF BILIARY STONES

Conventional Surgery

The standard treatment for gallbladder stones is cholecystectomy (surgical removal of the gallbladder), one of the commonest surgical procedures performed in Western countries. In Australia about 23,000 cholecystectomies are performed annually and the numbers appear to be increasing. Detailed data on the incidence of cholecystectomy in Australia are given in Tables 2 and 3.

Cholecystectomy is a major operation with significant morbidity. Mortality is low if it is performed as an elective procedure, but may be quite high if it is an emergency operation, particularly in elderly patients (13). For example, in a British series of 650 patients for whom cholecystectomy was performed as the sole biliary procedure, the mortality rate was 0.3%, (two deaths). The deaths (both patients over 80 years old) occurred only among emergency admissions (41 patients) and no deaths were reported after elective surgery (609 patients). About 30% of the patients experienced complications (14). Wound infection is a frequent complication. The Panel also understands tht in emergency operations there is a higher risk of damage to the duct or the right hepatic artery.

TABLE 2 : CHOLECYSTECTOMIES FOR WHICH MEDICARE BENEFITS HAVE BEEN PAID

State	1984/85	1985/86	1986/87
NSW	4 102	4 455	4 719
VIC	2 772	2 980	3 201
QLD	1 527	1 759	1 844
SA	1 121	1 296	1 361
WA	883	929	930
TAS	254	296	341
ACT	168	176	227
NT	28	36	45
TOTAL	10 855	11 927	12 668

Source: Commonwealth Department of Community Services and Health

TABLE 3 : CHOLECYSTECTOMIES ON PUBLIC PATIENTS IN PUBLIC HOSPITALS

State	1985		1986	
NSW	3 088		na	
VIC	2 605	(84/85)	2 706	(85/86)
QLD	1 674		na	
SA	1 220		1 181	
WA	1 012		1 122	
TAS	366		370	
ACT	149	(84/85)		
NT	na		na	
TOTAL (est)	10 140		na	

na: not available
Source: State and Territory Health Authorities

There is considerable controversy over whether cholecystectomy should be performed on asymptomatic patients. It appears that surgery in asymptomatic patients is justified only in particular circumstances, for example in the case of those with non-functioning gallbladders or numerous stones (6).

In the USA, the average hospital stay for cholecystectomy is 8.6 days (15). In Australia in 1985 average hospital stays for cholecystectomy were 12.6 days for men and 10.6 days for women (16). It may be four weeks before the patient can resume normal activities.

Cholecystostomy is a much less commonly performed procedure involving incision into the gallbladder and drainage of its contents. It is used in seriously ill patients considered at high risk for cholecystectomy, which is usually performed later, if the patient's condition has improved.

Cholecystectomy is frequently accompanied by surgical exploration of the common bile duct to locate and remove stones (choledochotomy). This operation may also be carried out as a separate procedure. It is performed if there is evidence of obstruction on a cholangiogram, if stones are palpable, or obstructive jaundice is present. Medicare and public hospitals data indicate that about 1600 choledochotomies are performed in Australia annually.

Exploration of the common bile duct has a high associated morbidity. For example, in a recent British series of 160 patients 46% developed complications, and the mortality rate was 2.5% (14). Wound infection and septicaemia are frequently complications.

Non-Surgical Forms of Treatment

Percutaneous Removal

Direct percutaneous catheterisation of the gallbladder is an alternative to surgical cholecystostomy for critically ill patients. Subsequently the tract can be dilated and the gallstones removed percutaneously (17, 18).
While this procedure may be advantageous for poor risk surgical candidates, its suitability for healthy patients is less certain. With appropriate precautions and in skilled hands it may have lower morbidity than cholecystectomy but the need for hospitalisation remains and in addition patients have the discomfort of a percutaneous tract for two weeks or more. The technique has the disadvantage that it does not overcome the problem of recurrence. Overall, it appears that the advantages of percutaneous techniques over conventional surgery for gallstones are not as clear as those for kidney stone removal.

Percutaneous extraction may be used as a post-operative procedure after cholecystectomy and bile duct exploration for the removal of retained bile duct stones. A T-tube inserted at operation is removed 6-8 weeks later and any retained stones extracted through the T-tube tract with a basket. This procedure is uncommon.

Chemical Dissolution

Chemical dissolution of biliary stones may be achieved by oral medication or by direct infusion of topical agents. Oral medication is undertaken with the bile acids chenodeoxycholic and ursodeoxycholic acid, previously discussed in this report in their role in association with ESWL. They are effective only with cholesterol stones and only in selected cases, depending on factors such as number of stones (3).

In the National Co-operative Gallstone Study, a randomised multi-centre, double-blind prospective study undertaken in the USA, daily use of a high dose of chenodeoxycholic acid for 2 years resulted in complete dissolution of gallstones in only 14% of patients (3, 5). A similar overall success rate hss been found in an Australian trial using chenodeoxycholic acid, but for patients with small multiple floating stones, a dissolution rate of up to 70% a year can be expected (Toouli, personal communication).

A major problem with dissolution therapy is that it does not cure the underlying condition, and gallstones can be expected to have recurred in up to 50% of patients within five years of treatment (19). Concerns have been expressed about the atherogenic effects of chenodeoxycholic acid, while other side effects include liver function abnormalities and diarrhoea (3, 10).

Several trials have been undertaken to compare the efficacy of ursodeoxycholic and chenodeoxycholic acid in the dissolution of gallstones. The results indicate that in comparison with chenodeoxycholic acid, ursodeoxycholate is equally or more effective, and has fewer side effects. Some data suggest that a combination of the two agents is more effective than either alone (3).

Given the problems of slow rates of dissolution, high recurrence rates and high costs (see page 20), it seems unlikely that oral bile acid therapy alone, without ESWL, will play a major role in the treatment of gallstones (20).

The dissolution of gallbladder and bile duct stones by direct infusion through a percutaneous T-tube or catheter has been attempted with a number of agents. Most have proved to be

too toxic or ineffective, and most attention is now focused on two substances, mono-octanoin and methyl-t-butyl ether. Both these agents are effective only with cholesterol stones.

In various studies on the use of mono-octanoin for the treatment of retained stones, complete dissolution has been achieved in 50-86% of cases with continuous perfusion for 3 to 7 days through a T-tube or transhepatic catheter. Side effects can include pain, respiratory distress, nausea and vomiting (3).

More rapid results are achieved with methyl-t-butyl ether, which dissolves cholesterol stones in 3-20 hours of continuous perfusion (20). Access to the gallbladder is by a percutaneous catheter (20). Side effects can include nausea, duodenitis, haemolysis, hepatic necrosis, and moderate anaesthesia (3, 20). The substance is flammable and requires electrically safe facilities for usage.

With treatment using either mono-octanoin or methyl-t-butyl ether, the problem of gallstone recurrence remains. It has been suggested that the methyl-t-butyl ether procedure is unlikely to come into general use but will remain available in larger centres (20).

Endoscopic Sphincterotomy

Endoscopic sphincterotomy can be used to clear the common bile duct of stones. Through a side-viewing duodenoscope, the common bile duct is cannulated and the papilla is enlarged with an electrocautery wire. Stones can be removed with the aid of a balloon or basket, but more usually pass spontaneously (3).

In skilled hands the success rate for the retrieval of stones by this procedure is in the region of 80-90%. The technique is available in most Australian teaching hospitals and is being used increasingly in this country. The Panel estimates that about 700 procedures were performed in Australia in 1986/87.

An overnight hospital stay is required with endoscopic sphincterotomy. The procedure has significant morbidity. Complications include bleeding and pancreatitis (20). Perforation is a rare but extremely serious complication. The mortality rate is around 1.5% (21).

EFFICACY OF GALLSTONE LITHOTRIPSY

Gallstones

Dornier have provided the Panel with data on 2,450 patients with gallbladder stones treated on Dornier machines in the Federal Republic of Germany to August 1988. The ESWL treatment was followed by bile acid therapy. Some of the information is summarised in Table 4.

TABLE 4: ESWL TREATMENT OF GALLBLADDER STONES ON DORNIER MACHINES

Total number of patients	2,450
Percentage with solitary stones	60%
Percentage with multiple stones	40%
Percentage with calcified stones	20%
Average stone size	17mm
Average number of shock waves per treatment	1,600
Average treatment duration	50mins
Analgesia	50%
No medication	50%
Patients with stones successfully fragmented	98%
Patients clear of fragments 6 months after ESWL	
- solitary stones	64% *
- multiple stones	28% *
Patients clear of fragments 12 months after ESWL	
- solitary stones	88% *
- multiple stones	62% *
Repeat ESWL rate	20%

* Note: data on fragment clearance would be based only on that proportion of the patients treated for the length of time given, not on all 2,450.

Source: Dornier medical information supplied by Hahn & Kolb (Aust) Pty Ltd

Sackman et al have reported more detailed results for 175 gallstone patients treated on Dornier lithotripters (22). Treatment was restricted to patients who were symptomatic, had no more than three radiolucent gallstones with diameters less than 30mm, and a functioning gallbladder with an open cystic duct. Of the 175 patients, 145 had a solitary gallstone and 30 had two or three stones. Bile acid therapy was administered from 12 days before ESWL to three months after disappearance of fragments.

Gallstones were successfully fragmented in 174 of the 175 patients. Follow-up examinations, in which abdominal ultrasonography was used to determine the presence of stone fragments, were performed at defined intervals. At the time of preparation of Sackman et al's paper, only 68 patients had been followed up for 8 - 12 months, and 15 for two years. The proportion of all patients free of stones at different follow-up periods are given in Table 5. The results may be too limited at this stage for firm conclusions to be reached on the rate of clearance of gallstone fragments, particularly after 12 months.

By applying the techniques of actuarial analysis to their data, the authors have estimated that freedom from stones after one year can be expected for 83% of patients with single stones up to 20mm in diameter, 72% of those with single stones of diameter 21-30mm, and 63% of those with two or three stones. The validity of these estimates is uncertain.

TABLE 5: DISAPPEARANCE OF GALLSTONE FRAGMENTS AFTER LITHOTRIPSY

Period from ESWL to follow-up (months) at follow-up	Number of patients seen	Number (%) of patients free of stones
0-2 months	151	46(32)
2-4 months	130	63(48)
4-8 months	112	70(63)
8-12 months	68	53(78)
12-18 months	34	31(91)
18-24 months	15	14(93)

Source: Ref. 22

Sackman et al state that combined ESWL/bile acid treatment is more effective than bile acid therapy alone, noting that with the combined treatment 92% of patients with gallstones up to 15mm in diameter were free of stones after 12 months therapy, while with bile acids alone 38% of patients in this category were free of stones after 12 months (22).

Pochon et al have given preliminary results for ESWL of 24 gallstone patients each with up to 10 stones, with diameters of 7-31mm, using a Technomed Sonolith device (23). The first 20 patients required general or epidural anaesthesia, but following the installation of a modified shock wave generator, the last 4 patients could be treated using sedatives only. Of 14 patients with single stones, successful fragmentation was achieved in 11 cases. For 10 patients with multiple stones, successful fragmentation was achieved in only 4 cases.

Hood et al have provided results of treatment of gallbladder stones in 38 patients on a Wolf piezoelectric lithotripter. Patients were symptomatic with up to three stones of minimum diameter 10mm, and had an open cystic duct. Successful fragmentation was achieved in 34 patients but 25 required more than one treatment. Up to five treatments were given. The procedure was painless and no analgesia was required. At the time of publication, all patients successfully treated were on bile acid therapy, but no results were available on the rate of clearance of fragments (24).

Bile Duct Stones

Several reports have appeared describing the treatment by ESWL of small numbers of patients with stones in the common bile duct. The Dornier MPL-9000 has been used in the treatment of 30 patients with common bile duct or intrahepatic stones that could not be removed by non-surgical means, because they were too large or impacted, or because of strictures in the common bile duct. Fragments produced by ESWL were passed spontaneously or removed endoscopically. In 24 cases the stones were successfully fragmented (25).

Renal lithotripters have been used with fluoroscopic visualisation, to fragment radio-opaque bile duct stones. In a brief report from the University of Mainz, preliminary results have been given for the treatment of 17 patients with bile duct stones, on a Siemens Lithostar renal lithotripter (26). Stones were successfully fragmented in 9 of 13 patients with common bile duct stones, and in all of 4 patients with intrahepatic stones.

In Australia, a Dornier HM3 Lithotripter has been used successfully to fragment bile duct stones in two elderly patients considered high surgical risks, whose stones could not be removed by endoscopic sphincterotomy or basket extraction (27).

COMPLICATIONS OF GALLSTONE LITHOTRIPSY

In the study on the Dornier lithotripter, 35% of patients experienced one or more episodes of biliary colic after ESWL and before disappearance of stone fragments (22). Since all patients suffered from biliary colic before the treatment, this should not strictly be regarded as a complication, but it could be disappointing for many patients to find that they may continue to experience pain for some time after ESWL. In the trial reported by Pochon et al, two out of 24 patients experienced biliary pain severe enough to require cholecystectomy. These cases were subsequently found to be suffering from chronic cholecystitis which the researchers believed had been aggravated by the ESWL treatment (23).

Other complications reported in the trial on the Dornier lithotripter were as follows (22):

- loss of gallbladder function (3%)
- mild pancreatitis (1.1%)
- skin spotting in the area through which the shock wave passed (14%)
- transient haematuria (3%).

Evidence of minor liver damage after ESWL treatment of four patients with common bile duct stones has been reported (28).

In the series of 38 patients treated on a Wolf lithotripter, immediate side effects were slight. They included transient haematuria in two patients, abnormal liver function in one, and skin spotting in four. One patient had an episode of acute pancreatitis six weeks after treatment (24).

Earlier experimental work on animals indicated that there was a significant risk of pulmonary haemorrhage associated with biliary lithotripsy. This complication has not yet been observed in clinical trials with humans (22). The Panel has been advised that some animal data suggest that ESWL may cause some damage to the gallbladder, and it would be important to assess gallbladder emptying before and after ESWL (Toouli, personal communication).

Published reports do not give any information on complications from bile acid therapy associated with gallstone lithotripsy. As noted on page 12, side effects of bile acids include liver function abnormalities, diarrhoea, and increases in serum low-density lipoprotein cholesterol (3, 10).

As noted on page 12, gallstones recur in up to 50% of patients within five years after completion of oral bile acid therapy. It seems likely that similar recurrence rates would

be observed for a combination of ESWL and bile acid therapy. At this early stage in the application of gallstone ESWL it could be optimistic to assume that all possible side effects and complications have been identified, particularly long term effects.

INDICATIONS FOR GALLSTONE LITHOTRIPSY

Gallbladder Stones

Given the very limited results available to date, it is too early for the indications for gallstone lithotripsy to be fully defined. However it is clear that treatment of gallbladder stones will require a functioning gallbladder and an open cystic duct to ensure that dissolution and clearance of fragments can occur. Results to date suggest that ESWL is applicable to patients with solitary gallstones and less so to patients with up to three stones (22). It may be ineffective if more than three stones are present in the gallbladder. If gallbladder stones are calcified they can be successfully disintegrated, but further information is needed to establish that the fragments can successfully be cleared. Care would need to be taken to exclude patients with conditions which could be aggravated by ESWL (23).

At present ESWL is being applied to symptomatic patients, but in the future there may be pressure to apply it to asymptomatic patients with the aim of preventing long term complications of gallstones. Such application appears unjustified on the basis of present data.

Bile Duct Stones

To date, ESWL has been applied to bile duct stones which could not be removed by surgical or endoscopic techniques, either because they were too large or impacted, or because of the condition of the patient (23, 27). It is possible that in the future these indications will be widened. Biliary ESWL may be particularly useful for the treatment of intrahepatic bile duct stones which are difficult to treat by surgical or endoscopic means (29).

COSTS OF GALLSTONE LITHOTRIPSY AND CONVENTIONAL SURGERY

Lithotripsy of Gallbladder Stones

Cost ranges for lithotripsy of gallbladder stones have been estimated for comparative purposes only, on the basis of prices at August 1988. The following assumptions have been used:

- the installed capital cost of the lithotripter is $A1.5 million and the cost of site preparation is $A50,000;

- capital costs are amortised over five years at 15% interest;

- servicing is provided free of charge in the first year and thereafter is provided at a cost equivalent to 9% of the capital cost; an annual figure is derived by averaging costs over the first five years;

- the lithotripter is operated by a specialist who receives a fee equivalent to that for renal stone ESWL;

- an anaesthetist is not required;

- the diagnostic procedures required before treatment are plain film X-ray, oral cholecystography, abdominal ultrasound, and urine and blood analyses (21);

- after treatment abdominal ultrasound and blood analysis are required every two months until fragments are cleared, which may require from two months to two years (22);

- medication with a combination of chenodeoxycholic and ursodexycholic acid is required until six months after fragments have cleared (30). The dose for each drug is 7-10 mg per Kg body weight per day and the weight range for patients is 50-100 Kg. The cost of chenodeoxycholic acid is $2.64 per gram, calculated on the basis of the cost for supply to hospitals ($30.97 per 100 capsules of 125 mg each with allowance for hospital dispensing costs); the cost of ursodeoxycholic acid in Australia is similar to that of chenodeoxycholic acid;

- costs of support staff for the ESWL unit (a nurse/receptionist and a technical assistant) amount to $70,000 a year, including salaries and on-costs;

- hospital costs (excluding costs of tests and ESWL treatment) are $310 a day. Day care costs are $180 a day.

Table 6 gives the components of the costs of gallstone lithotripsy based on these assumptions.

TABLE 6: COMPONENTS OF COSTS OF GALLSTONE LITHOTRIPSY

	$A
Annualised fixed costs	655,500
Annualised fixed costs per patient	
600 procedures a year	1,092
1200 procedures a year	546
Recurrent ESWL treatment costs per patient (including pre-treatment tests)	
- two days in hospital	1,168
- day care	728
Cost range for post-ESWL treatment (bile acid therapy and tests)	597 - 5,796

The cost range for ESWL of gallbladder stones is wide, principally as a result of the range of post-ESWL treatment costs, which cover bile acid medication and tests to check fragment clearance. Bile acid costs depend on the duration of therapy, and on the dosage rate which is determined by the body weight of the patient. To demonstrate the effect of post-ESWL therapy, Figure 1 gives costs for a single ESWL treatment (two days hospitalisation) at different rates of fragment clearance for a patient of 64 Kg, the mean weight of adult Australian women, and for a patient of 78 Kg, the mean weight of adult Australian men, at two different throughputs. (Mean weights are from National Heart Foundation data.)

Costs are sensitive to the price of bile acids. The costs used in these estimates ($2.64/gram) are based on the price of chenodeoxycholic acid supplied directly to hospitals. The price from pharmaceutical retailers is more than double this. Moreover, the assumption that ursodeoxycholic acid would be similar in price to chenodeoxycholic acid in Australia is uncertain. Figure 2 demonstrates how the cost of ESWL of gallbladder stones is affected by varying bile acid costs, for a 78Kg patient requiring 12 months for fragment clearance, treated on a machine with a throughput of 600 patients a year.

Other factors affecting costs are throughput, duration of hospitalisation and any need for repeat treatments. Table 7 and Figure 3 give estimated ranges of costs of gallbladder stone lithotripsy per patient at two different throughputs, for the following sets of conditions:

- one ESWL treatment only is required, and the patient is hospitalised for two days (as might be expected during the early stages of this technology);

- one ESWL treatment only is required and it is carried out on a day care basis (which may become possible as experience is gained);
- two ESWL treatments are required, the second for incomplete fragmentation, and a total of four days hospitalisation are required;
- two ESWL treatments and two courses of bile salt therapy are required, the second set of treatments being for recurrent stones.

In summary, major factors affecting the cost of gallstone lithotripsy are the period of bile acid therapy required, the costs and dosage of bile acids, and any need for repeat treatment. Capital costs, throughput and hospitalisation appear to be less significant factors.

TABLE 7: ESTIMATED COST RANGES FOR GALLSTONE LITHOTRIPSY

Type of Treatment	Cost Ranges $A	
	Throughput 600 procedures pa	Throughput 1200 procedures pa
One treatment 2 days hospitalisation	2,900 - 8,100	2,300 - 7,500
One treatment, day care	2,400 - 7,700	1,900 - 7,100
Two treatments incomplete fragmentation	5,100 - 10,300	4,000 - 9,200
Two treatments, recurrent stones	5,700 - 16,100	4,600 - 15,000

FIGURE 1: EFFECT OF FRAGMENT CLEARANCE RATES ON COSTS OF GALLSTONE LITHOTRIPSY

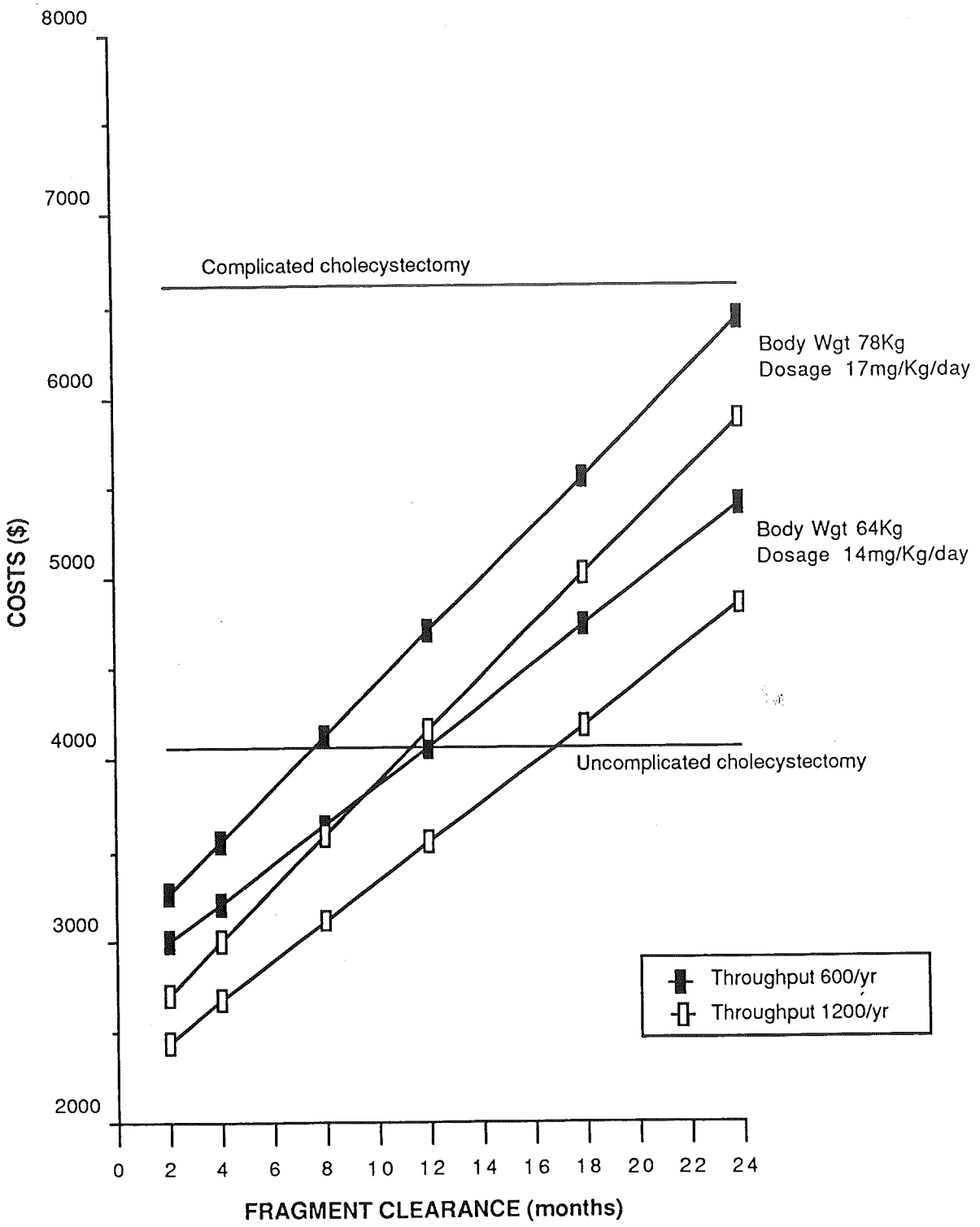


FIGURE 2: EFFECT OF BILE ACID COST ON COST OF GALLSTONE LITHOTRIPSY

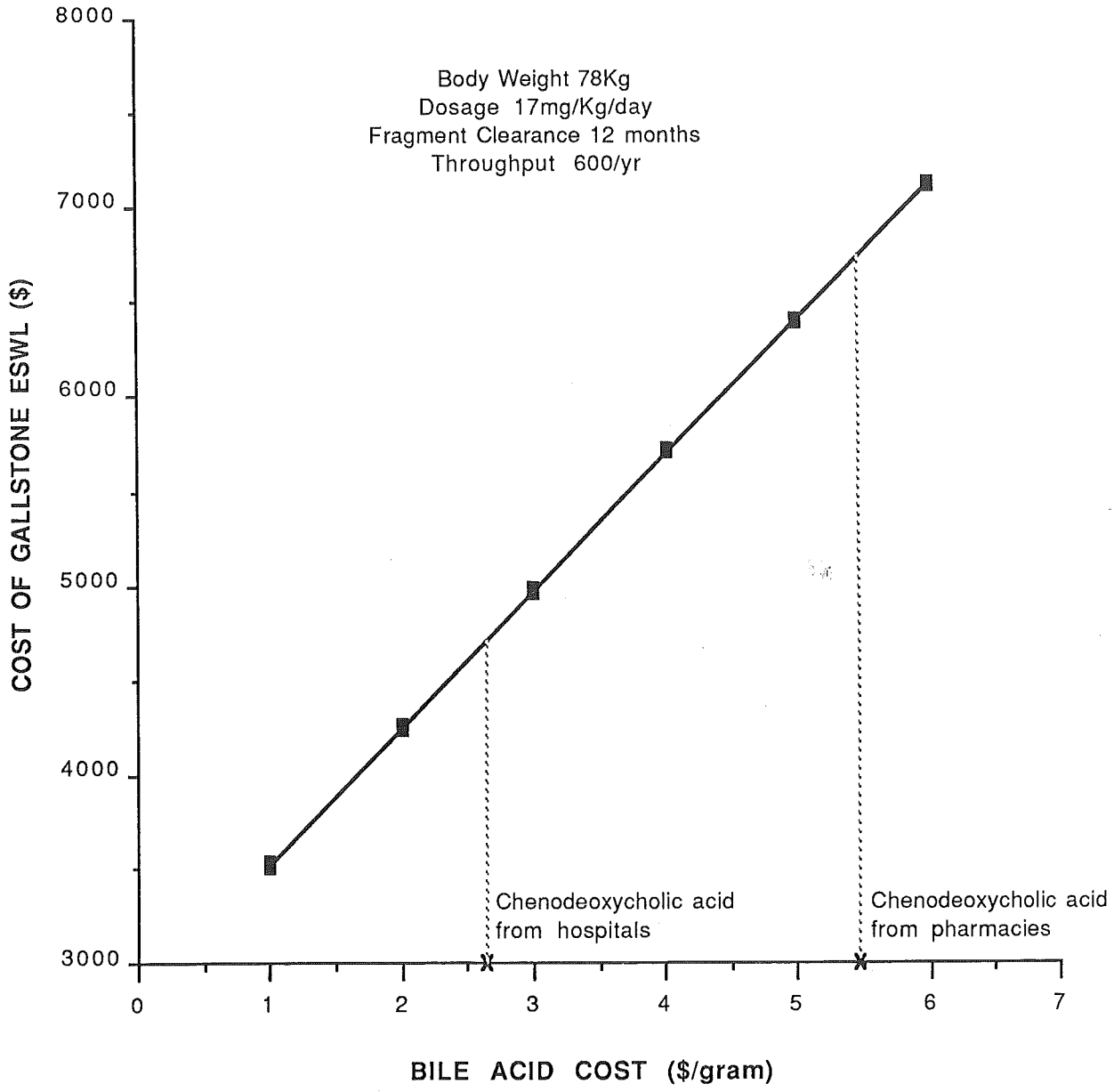
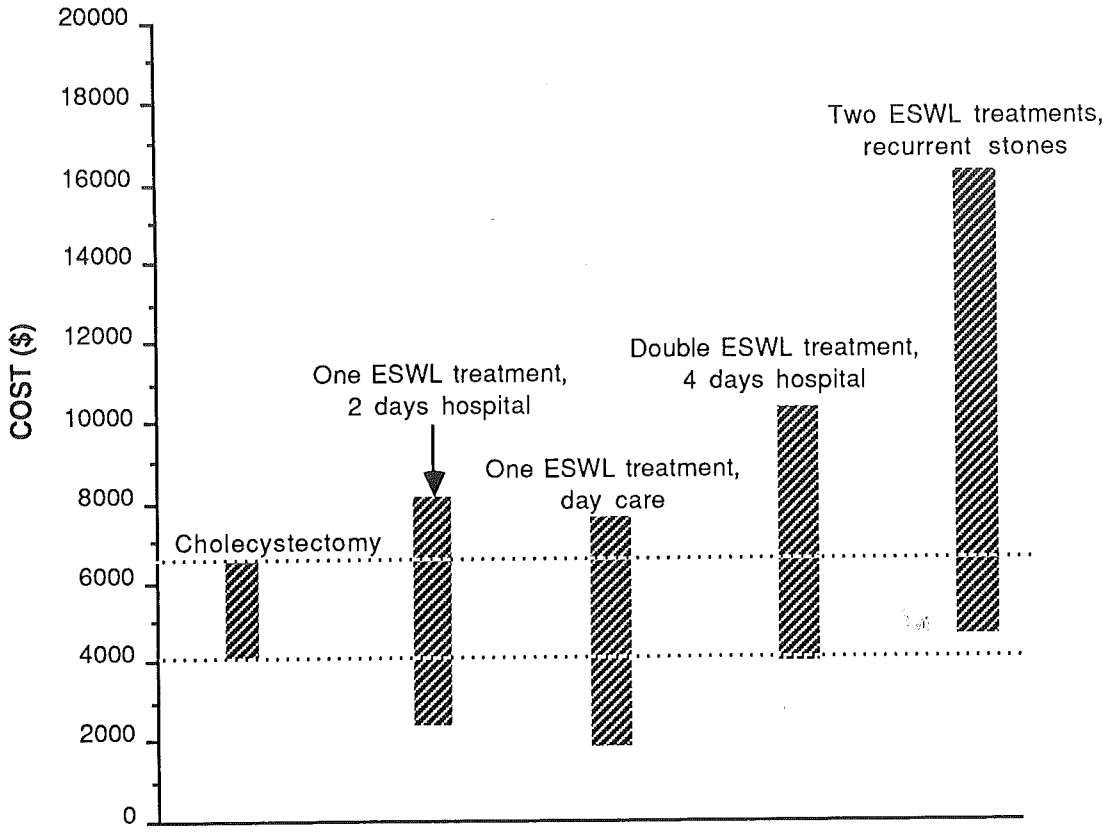


FIGURE 3: ESTIMATED COST RANGES FOR GALLSTONE LITHOTRIPSY AND CHOLECYSTECTOMY



Cholecystectomy

Table 8 gives an estimate of the cost of straightforward cholecystectomy without complications, based on the following assumptions:

- the procedure is performed by a specialist surgeon with an assistant and an anaesthetist;
- bile duct exploration is not performed;
- diagnostic procedures used are plain film X-ray, oral cholecystography, operative cholangiogram, ultrasound, and urine and blood analyses (pre- and post-treatment);
- there are no complications requiring additional procedures
- 8 days in hospital are required.

TABLE 8: COST OF CHOLECYSTECOMY

Item	Cost ($)
Surgeon's fee	445
Assistant's fee	52
Anaesthetist's fee	120
Theatre costs	600
Hospital costs	2480
Diagnostic procedures	358
Medication	20
Total:	4,075

If there are complications, the length of hospital stay will be increased, and additional tests and medication may be required. If the hospital stay is 15 days, the cost of complicated cholecystectomy is estimated to be $6,615.

Comparison of Costs of Gallstone Lithotripsy and Cholecystectomy

The cost of cholecystectomy is compared with cost ranges for gallstone lithotripsy in Figures 1 and 3. The data suggest that in many cases, gallstone ESWL will have a cost advantage over uncomplicated cholecystectomy. However, the cost advantage will be lost if extended periods of treatment with bile acids are required. The range of patients for whom gallstone ESWL has a cost advantage is increased substantially if it is compared with surgery involving a longer hospital stay or additional procedures.

Gallstone lithotripsy has the advantage over cholecystectomy that the recovery period is much shorter. For gallstone ESWL, the period of absence from normal activity may be only one week, while for cholecystectomy it is likely to be four weeks. If the social cost of such absence from normal activity can be expressed in terms of earnings lost, the offsetting savings for the lithotripsy procedure, estimated on the basis of Australian average weekly earnings in August 1988 (31), would notionally be in the region of $1,250. By taking this sum into account, the proportion of gallstone lithotripsy cases that would have a cost advantage over cholecystectomy would be significantly increased.

Several factors would tend to reduce the off-setting saving. They would include any absences from work during the period of bile acid therapy, as a result of side effects or for tests and consultations, and absences from normal activity as a result of repeat treatments required for recurrent stones.

The Panel has estimated the costs of treating 2300 patients with gallbladder stones (10% of all candidates for cholecystectomy) by gallstone lithotripsy and by cholecystectomy. These figures were chosen to give an indication of comparative national costs at this level of substitution. The estimates involve a number of approximations and are based on assumptions most of which are very uncertain at this early stage. The results should be regarded as only indicative of the possible relationship between costs for the two procedures. The assumptions are:

- 70% of the patients are women and 30% are men;
- average body weights are 64 kg for women and 78 kg for men;
- average bile salt dosages are 14 mg/Kg/day for women and 17 mg/Kg/day for men;
- 30% of patients are free of fragments 2 months after ESWL, a further 20% after 4 months, 15% after 8 months, 15% after 12 months, 10% after 18 months, and 10% after 2 years (these figures are based on the results of Sackman et al [20]);
- 80% of patients require a single ESWL treatment and 20% a second treatment for incomplete fragmentation;
- for cholecystectomies, 70%-80% are uncomplicated and require an average 8 days hospitalisation, while 20%-30% have complications and require an average 15 hospital days;
- no other biliary procedures are performed.

These assumptions give a total cost range for gallstone lithotripsy of $8.4M - $9.9M at throughputs of 600-1200 procedures a year. For cholecystectomy total costs are in the range $10.5M - $11.1M. If costs of delayed return to normal activities are taken into account, the estimates for gallstone lithotripsy rise to $9.4M - $10.8M, and for cholecystectomy to $14.3M - $14.9M.

These results suggest that overall, gallstone ESWL may have a cost advantage compared with cholecystectomy. However, if requirements for repeat treatment for recurrent stones are taken into account the cost advantage may be reduced or lost.

For example, if complete repeat treatments for recurrent stones are required for 50% of patients, the total costs of gallstone ESWL on this model rise to $14.1M - $16.2M if delayed return to normal activity is taken into account.

The relative position of cholecystectomy would also improve if fragment clearance rates are slower than assumed in this model, or if complication rates for cholecystectomy are lower.

Lithotripsy of Bile Duct Stones compared with Choledochotomy

The cost of lithotripsy of bile duct stones was estimated on the basis of the following assumptions:

- costs of the lithotripter, hospital charges and specialists' fees are as for gallstone lithotripsy;
- two to four days hospitalisation are required;
- pre-treatment diagnostic procedures required are endoscopic retrograde cholangiopancreatography, X-ray, abdominal ultrasound, and urine and blood analysis;
- stone fragments are passed spontaneously;
- abdominal ultrasound and blood analyses are performed after treatment;

These assumptions give estimated cost ranges for lithotripsy of bile duct stones of $2,700 - 3,300 at a throughput of 600 procedures a year, and $2,100 - 2,800 at a throughput of 1200 a year. These estimates do not include the cost of endoscopic sphincterotomy (approximately $670 including the procedure and an extra day in hospital) which may often be associated with the lithotripsy procedure. If endoscopic retrieval of fragments is required, the cost may be increased by about $420 (including cost of the procedure plus an additional day in hospital). With these procedures added, the total cost range becomes $3,200 - $4,400.

By comparison, the cost of choledochotomy (as a separate procedure from cholecystectomy) would be in the region of $4,400 if it is assumed that it is uncomplicated and that eight days hospitalisation are required. With complications the cost may rise close to $6,900. These estimates suggest that lithotripsy may usually have a cost advantage over choledochotomy for the removal of bile duct stones. It would not be expected to have a cost advantage over endoscopic sphincterotomy and retrieval of stones, which may have a total cost as low as $1700 (including hospitalisation and associated diagnostic tests). Biliary ESWL is more likely to be used as an adjunct to endoscopic sphincterotomy than an alternative.

ROLE OF GALLSTONE LITHOTRIPSY IN HEALTH CARE

Comparison of Gallstone Lithotripsy and Cholecystectomy

It is questionable whether lithotripsy of gallbladder stones can be strictly considered an alternative to cholecystectomy. On current indications, most candidates for cholecystectomy would not be suitable for the lithotripsy procedure. For example, it could not be applied to patients with more than three or four stones. Estimates of the proportion of cholecystectomy candidates who could be treated by ESWL vary from 6% (32) to 25% (31).

In addition, gallstone ESWL is not equivalent to cholecystectomy in outcome. In particular, it is not curative, and eventual recurrence of stones is likely. Moreover, the lithotripsy procedure itself is only part of a prolonged treatment regimen.

For those patients who would be suitable, ESWL of gallbladder stones would have the advantages that it is a less invasive procedure, open surgery and general anaesthesia are avoided, and recovery is more rapid. Although insufficient data are available for definitive statements on complication rates, morbidity and mortality would probably be lower with the lithotripsy procedure.

If the results of further trials confirm the promising early data, lithotripsy will have a valid role in the treatment of a limited number of symptomatic patients with gallbladder stones, but at least in the short term it is unlikely to replace a substantial proportion of cholecystectomies.

Gallstone lithotripsy could be used as an additive procedure for patients for whom surgery is contra-indicated and who are being treated with bile acid therapy. In that situation it would be an additional cost to health care (34).

In the future the technology might be applied to asymptomatic patients or those with very mild symptoms only uncertainly associated with gallstones, who would not be considered for cholecystectomy. In these circumstances too, it would be an additional cost to health care. The potential cost of such

applications could be substantial, while their value would be uncertain, particularly given the likelihood of recurrence of stones.

Lithotripsy of Bile Duct Stones

It is likely that ESWL will have a limited but useful role in the management of retained bile duct stones, as one of a range of techniques. Present evidence suggests that it would be a feasible alternative to choledochotomy or percutaneous techniques for the removal of stones which cannot be removed endoscopically after sphincterotomy, because of their position or size. It would complement endoscopic sphincterotomy but would not replace it. The Panel has been advised that only one to two patients in every 100 treated by endoscopic sphincterotomy would require ESWL treatment (Fletcher, personal communication).

Providers of Gallstone Lithotripsy

In its 1985 report, the NHTAP concluded that it was appropriate for renal stone ESWL to be operated by urologists (1). It is much less clear which specialty should provide gallstone ESWL (15). General surgeons have most commonly been responsible for the treatment of gallstones, by cholecystectomy, and in some Australian centres undertake endoscopic procedures in the biliary tract. Gastroenterologists have a strong interest in hepatobiliary disorders and also undertake endoscopic procedures in the biliary tract, while interventional radiologists as well as physicians are involved in the use of percutaneous procedures. Urologists are the group with most experience in the use of ESWL, but would be more likely to act as advisers than as direct providers of gallstone ESWL.

A provider of gallstone lithotripsy would need a sound understanding of the physiology and anatomy of the biliary tract, a capacity to deal with any complications that might arise, and considerable skills in the demanding area of ultrasound imaging. Some cooperation between specialties may be necessary. While it might be feasible for a lithotripter to be operated by a multi-disciplinary team, the institution providing the ESWL service would need to have a range of expertise available for back-up if required. This should include imaging, endoscopic and surgical expertise.

CONCLUSIONS

Present evidence indicates that gallstone ESWL is a promising modality for the treatment of patients who have up to three gallbladder stones, a functioning gallbladder and an open cystic duct. However, it does not appear that ESWL of gallbladder stones will have the clear advantages over conventional surgery

achieved by renal stone ESWL. Gallstone ESWL is applicable only to a limited proportion of patients. It is not equivalent to surgical removal of the gallbladder in that it does not provide a permanent cure, and its advantages in terms of reduced morbidity are less marked, since cholecystectomy involves lower operative risk than kidney stone surgery.

In many cases, gallstone ESWL could have a cost advantage compared with surgery. In cases requiring very prolonged treatment with higher dosages of bile salts, the cost advantage would be lost. For a population of suitable patients the overall costs of gallstone ESWL may be lower than for cholecystectomy. However, a need for repeat treatments and its use with patients who would not be considered for surgery could result in its being an additional cost to health care.

It is likely that ESWL will have a clinically useful role as an adjunct to endoscopic sphincterotomy in the treatment of difficult stones in the common or intra-hepatic bile ducts, which would otherwise require high risk surgery.

At this stage the Panel does not consider that sufficient data are available to justify the routine clinical use of ESWL for stones in the gallbladder or bile ducts. Questions remain on the failure rates, complications and long-term side effects of the ESWL treatment, the time required for bile acid therapy and its side effects, and recurrence rates for gallstones. It would not be in the interests of patients for the technology to be routinely used until these questions have been satisfactorily answered.

The Panel suggests that until much more information is available, gallstone ESWL should be considered for use in Australia only in the context of a prospective clinical trial with a well designed protocol. No more than one investigational unit would be justified at this stage. The trial should be undertaken in a major hospital by a team with highly developed expertise in biliary disorders, a capacity to understand ultrasound images, and demonstrated ability to undertake clinical evaluation. Appropriate imaging, endoscopic and surgical expertise should be available to tne unit as back-up.

The Panel notes that the application of gallstone lithotripsy to asymptomatic patients is an issue which will need to be considered carefully if its routine clinical use becomes established.

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