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Experimental Gallstone Dissolution with Methyl-Tert-Butyl Ether (MTBE) and Transcutaneous Ultrasound Energy

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The simultaneous application of ultrasound energy greatly accelerated the rate of cholesterol gallstone dissolution by methyl-tert-butyl ether (MTBE). In vitro experiments using this treatment showed that a 498-mg stone burden could be dissolved in 19.5 minutes, approximately 100% faster than what could be achieved with MTBE alone. Pigs (n = 13) with surgically implanted gallstones were treated with MTBE and transcutaneously applied ultrasound from a prototype system built for clinical studies. The average stone reduction of all pigs was 470.46 mg ± 60.44 mg; 91.39% of an average implanted burden of 515.08 ± 18.03 mg. Control group pigs (n = 9), receiving only an MTBE infusion, showed an average stone reduction of 51.77%. Enzymes indicative of hepatocellular injury showed no significant abnormalities after 6 weeks. Gallbladder ablation with a fibrous remnant (ie, no mucosa, no lumen, patent cystic duct) occurred in 10 (70%) of the pigs.

Key words: gallstone dissolution; ultrasound.

ATTEMPTS TO dissolve cholesterol gallstones date from 1891 when Walker[1] described the first dissolution of a stone by using diethyl ether. Since that time many attempts have been made to provide the safest and most reliable method of treating cholelithiasis by infusion of other solvents.[2] Mono-octanoin[3,4] and methyl-tert-butyl ether (MTBE)[5–7] have recently been used.

In addition to safety and efficacy, a major concern of any proposed treatment is the time necessary to achieve significant results. Experience with mono-octanoin points to a disappointing rate of dissolution of up to 21 days.[8–13] MTBE, in contrast, has been shown to act significantly faster than mono-octanoin.[14] McGahan et al[15] demonstrated that surgically implanted gallstones in swine can be dissolved with three to seven days of continuous MTBE infusion. Thistle's experience from the Mayo Clinic[16] showed that to achieve 95% dissolution, an average of two days of therapy was necessary, with an average of 12 hours of MTBE injections occurring over those two days.

Therapeutic ultrasound energy has been shown to enhance the cholelitholytic activity of mono-octanoin.[17] It was postulated therefore that a similar effect would occur with MTBE. This method, which would reduce the treatment time necessary, was evaluated in vitro and in a swine model.

Materials and Methods

Five pairs of human cholesterol gallstones, each pair from a different patient, were obtained from the pathology departments of local hospitals after cholecystectomies. Based on visual inspection and comparison to a subset of stones analyzed radiographically and by x-ray diffraction and infrared spectroscopy, stones having high calcium or pigment content were excluded. The stones were stored in a solution of 10% tincture of Zephiran (Benzalkonium chloride 1:750, Winthrop Laboratories, New York, NY) in normal Ringer's solution. This enabled hydration of the stones and

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minimized bacterial growth. Each pair of stones was divided: one experimental and one control stone from each pair.

Each single gallstone was placed into a separate latex finger cot containing approximately 7–10 cc spectrophotometric grade MTBE. An experimental laboratory prototype system (Fig. 1) was used to deliver ultrasound energy (frequency = 219 kHz; spatial-peak-temporal-average intensity of 3 w/cm^2, which is equivalent to 2.94 bars) to the experimental group stones while submersed in a 37° C degassed water bath. Both the ultrasound-treated stones and the control group stones were maintained in the water bath for the same elapsed time.

Stone dissolution across time of both the control and experimental groups was assessed by weighing (to the nearest 1 mg) each gallstone (or remaining fragments) before immersion into MTBE and at 6.5-minute intervals throughout the treatment. It was established by multiple, independent weighings of the same sample that weighing to the nearest 1 mg showed a 4% to 5% variability. Graphic representation of the rate of stone dissolution was obtained by plotting the remaining gallstone weight vs. elapsed time in minutes. A Student's t test at each time interval was used to establish significance at $P < 0.05$.

Young domestic pigs (n = 13) were used as an in vivo model of cholelithiasis. The preparation and use of this model, in which preselected and preweighed gallstones are surgically placed into the gallbladder, has been previously described.[18]

Before ultrasound treatment, the pigs were kept without food or water for 24 hours. Halothane (5%) was used as a general anesthetic. The hair in the right upper quadrant of the abdomen was removed.

A Toshiba diagnostic system (model SSA-90A) was used to obtain images of the pig's gallbladder and implanted stones. Under ultrasound guidance (Toshiba model GCE-406M), a 4F, extruded-nylon pigtail catheter was placed into the gallbladder.[18] The metal hub of the catheter was connected to a metal three-way stopcock to allow withdrawal of bile and infusion/withdrawal of MTBE.

The pig was secured in a supine reclining position on a cradle consisting of a water-filled cushion coupled to a large reservoir of sound-absorbing oil. A clinical prototype device was used to apply ultrasound energy (frequency = 219 kHz) to this experimental group of pigs. This device produces ultrasound energy that travels through a degassed water-filled applicator tube. Calibration of this device was achieved on the day of each experiment with a stainless steel ball radiometry method[19,20] as well as a total power output measurement using a pan balance. A flexible Mylar diaphragm at the distal end of the applicator was coupled to the pig's abdomen with ultrasonic gel. An in-line 3.75-MHz transducer (Toshiba model PSE-37H) was used to locate the gallstones in situ. Figure 2 shows the major components of this system. Once the applicator was properly aligned and fixed in a rigid position, the imaging transducer was removed and a therapeutic ultrasound transducer was positioned colinearly.

After accurate placement of the ultrasound applicator, bile was replaced with a bolus injection of approximately 7–8 cc of MTBE. MTBE was handled in glass syringes and contacted only nonleachable materials. Adequate ventilation was maintained and care was taken to avoid spillage or leakage that could produce MTBE vapor. During the ultrasound application, the MTBE in the gallbladder was removed and replaced with a fresh bolus of MTBE every 10 minutes.

Ultrasound with spatial-peak-temporal-average intensity of 3 w/cm^2 was applied to the gallstones of the pigs. A computer controlled the temporal delivery of this energy during the total elapsed time by using a 15.4% cycle of time on/total time of each cycle. This fractionation allowed for the dissipation of any potential heat buildup

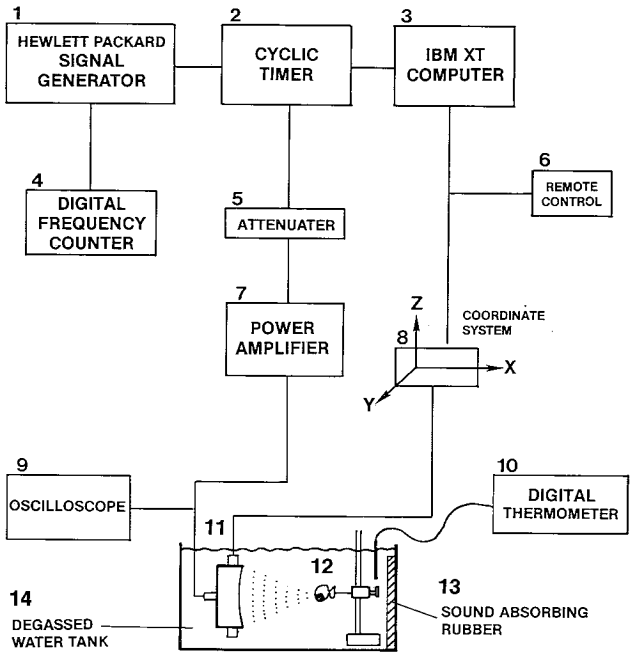


Fig. 1. Block diagram of experimental in vitro system. Major components include (1) Hewlett-Packard signal generator, (2) Harvard Apparatus cyclic timer, (3) IBM XT computer, (4) Heath-Zenith digital frequency counter, (5) an attenuator, (6) remote control, (7) ENI power amplifier, (8) X-Y-Z coordinate positioning system, (9) Tektronix oscilloscope, (10) digital thermometer, (11) ultrasound transducer, (12) test enclosure with MTBE and gallstone, (13) sound-absorbing rubber, and (14) tank full of degassed, deionized water.

in the transducer-applicator or the pig. The total elapsed treatment time for each pig was 97.5 minutes.

At the end of the treatment, all MTBE was aspirated from the gallbladder followed by repeated flushing with sterile lactated Ringer's solution.

The 13 experimentally treated pigs were sacrificed: three immediately after the treatment, one after one week, three after two weeks, three after four weeks, three after six weeks. Any remaining stones or fragments were removed and weighed.

To assess the potential risks involved in this procedure, blood enzymes indicative of liver damage were assayed. Blood samples were drawn before and after treatment and at one-week intervals until the animals were sacrificed. Samples were analyzed by SMAC 24 for SGPT, SGOT, lactic dehydrogenase (LDH), alkaline phosphatase, total bilirubin, and cholesterol concentrations, and the albumen:globulin ratio. A series of 13 paired t tests was implemented to detect differences across time for each of the seven blood parameters. These 13 tests evaluated pretreatment vs. all other times and posttreatment vs. all other times. Only pigs still alive at a given posttreatment interval were included.

In addition to blood tests, the gallbladder and adjacent tissues were examined grossly and necropsied for histopathologic evaluation. After staining the slide specimens with hematoxylin and eosin, we examined these tissues under the light microscope for edema, coagulative changes, acute or chronic inflammation, and fibrosis. A board-certified pathologist scored each sample (with reference to normal tissue) on a qualitative scale of 0 to 5, with 0 being normal and 5 being the highest. The scores for each

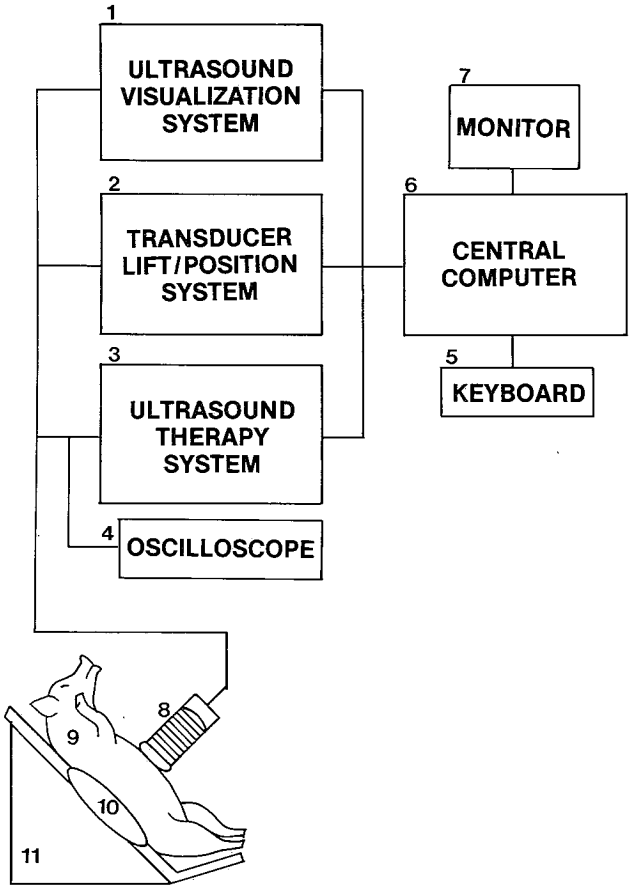


Fig. 2. Block diagram of experimental in vivo system. This integrative system consists of (1) a commercially available ultrasound visualization system (Toshiba model no. SSA-90A), (2) a transducer lift and positioning system, and (3) the ultrasound therapy system. (Major components are similar to the in vitro system detailed in Figure 1.) A central computer (6) controls the interactions between these components. User interface is achieved with a keyboard (5) and a monitor (7). An oscilloscope (4) is also included for calibration purposes and monitoring of ultrasound output. The ultrasound therapy and visualization transducer are housed within the applicator head (8), which is coupled to the pig (9). The pig is positioned on a pillow filled with degassed water (10) that, in turn, is supported on a cradle (11) of sound absorbing oil.

pathologic appearance were analyzed separately using two-way analysis of variance (ANOVA). The two-way ANOVA considered both treatment (MTBE vs. ultrasound and MTBE) and posttreatment time (ie, two, four, or six weeks) as independent factors.

A control group of nine pigs was handled in exactly the same manner as the experimental group with the omission of the ultrasound application. Three control animals were killed immediately, two after two weeks, two after four weeks, and two after six weeks. A Student's t test was used to compare the gallstone reduction in the treated group with the reduction in its respective control group. Statistical significance was considered to be $P < 0.05$. A comparison of the stone reduction was also made between the control and experimental groups irrespective of the time until sacrifice.

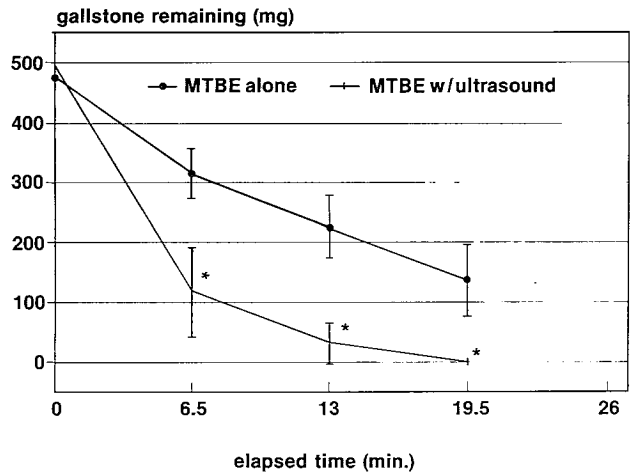


Fig. 3. The effect of ultrasound on the cholesterol gallstone dissolution by MTBE: in vitro results. Experimental gallstones (n = 5, +) were treated with MTBE and ultrasound. Matched control stones (n = 5, •) received only MTBE treatment. Periodic weight measurements were taken. Statistical significance (denoted by an asterisk) ws established at $P < 0.05$ Data points represent the mean ± 1 SEM.

Results

The in vitro experiments were summarized into a graph showing the remaining gallstone mass over the elapsed time of the experiment (Fig. 3). To minimize any effect that might be due to size or surface area variation, all stones selected had initial weights of approximately 500 mg. Stones in the control group's average initial weight was 477.6 mg ± 30.5 mg and the experimental group's average initial weight was 498.0 mg ± 24.1 mg (mean ± SEM). Each of the ultrasound-treated stones was totally dissolved after 19.5 minutes. This corresponded to 3 minutes of total ultrasound exposure delivered by a 15.4% duty cycle as described previously. The stones in the control group, on the other hand, lost an average of 274.50 mg ± 114.8 mg in the same elapsed time. With the exception of the initial weights, there were statistically significant differences ($P < 0.05$) between the control group and the experimental group at each measurement time period.

Table 1 summarizes the experience with the 13 experimentally treated pigs. The average absolute stone reduction was 470.46 mg ± 60.44 mg (91.39% ± 11.72%); the range was 70.4% to 100% stone dissolution. This can be compared with the control group of nine pigs (Table 2). The average absolute stone reduction in this group was 271.9 mg ± 128.2 mg (51.77% ± 24.50%) with a range of 38 mg (7.6%) to 457 mg (90.5%).

Statistical significance ($P < 0.05$) was established for each posttreatment period between the control and experimental groups for both absolute (mg) stone reduction and percentage stone reduction, with two exceptions. The pigs that were sacrificed at four weeks had a significance level of $P = 0.0630$ for percentage weight reduction. The pigs that were sacrificed

TABLE 1. In Vivo Treatment Group (MTBE and Ultrasound)

Pig No.	No. of Stones Implanted	Total Weight of Stones (mg)	Posttreatment Time (weeks)	Stone Reduction (mg)	Stone Reduction (%)
1	3	539	0	446	82.7
2	2	536	0	536	100.0
3	4	518	0	446	86.1
4	1	513	1	400	78.0
5	4	495	2	495	100.0
6	3	502	2	502	100.0
7	5	524	2	380	72.5
8	2	551	4	551	100.0
9	3	505	4	497	98.4
10	8	514	4	514	100.0
11	7	491	6	491	100.0
12	2	506	6	356	70.4
13	2	502	6	502	100.0

Averages ± 1.0 SD for various parameters of interest: no. of stones implanted, 3.5 ± 2; total weight of stones, 515.08 mg ± 18.03 mg; absolute stone reduction (mg), 470.46 mg ± 60.44 mg; percentage stone reduction, 91.39% ± 11.72%.

at six weeks had a significance level of $P = 0.0803$ for absolute (mg) weight loss. If the data are analyzed irrespective of posttreatment period, then the statistical significance level between the two groups is $P = 0.000042$ for absolute (mg) reduction and $P = 0.000028$ for percentage reduction.

The blood parameters assayed showed no statistically significant elevations (up to six weeks posttreatment) after adjustment of the P values for multiple testing based on the Bonferroni inequality. Those tests thqat were nominally significant before adjustment involved alkaline phosphatase (pretreatment vs. posttreatment, $P = 0.02$; and posttreatment vs. week 1, $P = 0.005$) and LDH (posttreatment vs. week 1, $P = 0.009$; week 2, $P = 0.007$; week 3, $P = 0.02$; and week 4, $P = 0.02$). The temporal variations in the blood levels of alkaline phosphatase and LDH are given in Table 3.

These differences, all of which involve the posttreatment measure for alkaline phosphatase and LDH, may result from chance alone (as the adjustment for multiple testing indicates), but they suggest that they are the result of a rise in these enzyme levels immediately after treatment. Regardless, these enzyme levels returned to their pretreatment levels after four weeks.

Histologic sections were prepared from the gallbladder, liver, and skin with attached abdominal wall of each pig. The pathologist's scoring for edema, coagulative changes, acute and chronic inflammation, and fibrosis of the livers from both the experimental group and the control group showed no observable effect and, therefore, no statistical analysis was performed. In considering the three control pigs' gallbladders that were scored, the first showed no changes in any of the parameters analyzed, the second showed only minor (1+) acute inflammation, and the third showed some chronic inflammation (1–2+) and minor fibrosis (1+). Differences were detected in the gallbladders examined for acute inflammation, chronic inflammation, and fibrosis. In considering acute inflammation, a difference ($P = 0.094$) between the control and experimental groups was detected. For chronic inflammation, a significant interaction ($P = 0.030$) was detected between the treatment and the posttreatment time intervals. Fibrosis scores were significantly higher ($P = 0.0003$) for the experimental group than the control group. Figure 4 shows

TABLE 2. In Vivo Control Group (MTBE Infusion Only)

Pig No.	No. of Stones Implanted	Total Weight of Stones (mg)	Posttreatment Time (weeks)	Stone Reduction (mg)	Stone Reduction (%)
14	3	501	0	38	7.6
15	2	537	0	183	34.0
16	3	530	0	358	67.5
17	4	514	2	322	62.6
18	1	505	2	189	37.4
19	2	505	4	457	90.5
20	3	543	4	321	59.1
21	2	549	6	372	67.8
22	2	502	6	198	39.4

Averages ± 1.0 SD for various parameters of interest: no. of stones implanted, 2.4 ± 0.9; total weight of stones, 520.7 mg ± 19.1 mg; absolute stone reduction (mg), 270.9 mg± 128.2 mg; percentage stone reduction, 51.77% ± 24.50%.

TABLE 3. Enzyme Levels of the Treatment Group (MTBE and Ultrasound)

Sampling Time	Enzyme (U/l) Alkaline Phosphatase	Lactic Dehydrogenase
Pretreatment (n = 9)	148.33 ± 54.36	413.00 ± 52.39
Posttreatment (n = 9)	161.55 ± 48.26	611.44 ± 153.46
Week 1 (n = 9)	139.33 ± 41.07	438.89 ± 101.11
Week 2 (n = 8)	159.13 ± 35.98	396.50 ± 61.61
Week 3 (n = 6)	165.67 ± 51.81	481.00 ± 57.40
Week 4 (n = 6)	173.50 ± 62.06	410.33 ± 120.49
Week 5 (n = 3)	142.67 ± 22.12	433.00 ± 35.16
Week 6 (n = 3)	154.67 ± 26.42	520.00 ± 205.25

the average relative pathology profiles for each of the experimental pigs' gallbladders.

These fibrotic effects on the gallbladder were reflected in the gross appearance of this organ as seen in Figure 5. Seven of the ten pigs killed at one week or later demonstrated gallbladder ablation (ie, a fibrotic mass of scar tissue with no lumen, no mucosa, and a normal, patent cystic duct). None of the control pigs showed this gallbladder ablation.

Minor skin irritations were common immediately after ultrasound exposure. These irritations were areas of reddening where the diaphragm of the ultrasound applicator was coupled to the skin with ultrasonic gel. Histologic analysis of these areas showed minor inflammation (1+) and significant fibrosis (3+) in all three of the animals sacrificed at two weeks. Only one of the animals sacrificed at four weeks showed fibrosis (3+) and inflammation (1+). The three pigs killed at six weeks showed no observable effect grossly or histologically.

Discussion

In considering the direct infusion of solvents to treat gallstones, the length of treatment time is always a critical factor. Both mono-octanoin and MTBE previously have been reported to be effective solvents for cholesterol gallstones. Clinical and laboratory data indicate that MTBE is both faster acting[14] and safer[15,21–23] than mono-octanoin. Therefore, MTBE is currently preferred.

In an earlier study, we found that the simultaneous application of therapeutic ultrasound energy enhances the dissolution property of mono-octanoin tenfold.[17] The current study indicates that a similar phenomenon occurs when ultrasound is applied simultaneously with MTBE infusions.

In vitro data showed that a gallstone burden of approximately 500 mg can be dissolved in MTBE in fewer than 20 minutes when an ultrasound field is used. This is 50% faster than what we achieved with a combination of mono-octanoin and ultrasound. In contrast to classical shock-wave lithotripsy, the gallstones treated with ultrasound and MTBE did not shatter or fragment instantaneously. Rather, they dissolved with the cholesterol rapidly going into solution. Inevitably during this process, the single stones fell apart into smaller stones, but the primary mechanism of the ultrasound was not simply to shatter the stones yielding a larger surface area for action by MTBE. Although this level of in vitro effectiveness was encouraging, in vivo evaluations were necessary to assess not only efficacy but also safety.

Of the 13 pigs treated with MTBE and ultrasound, seven were completely stone-free and the average stone burden loss

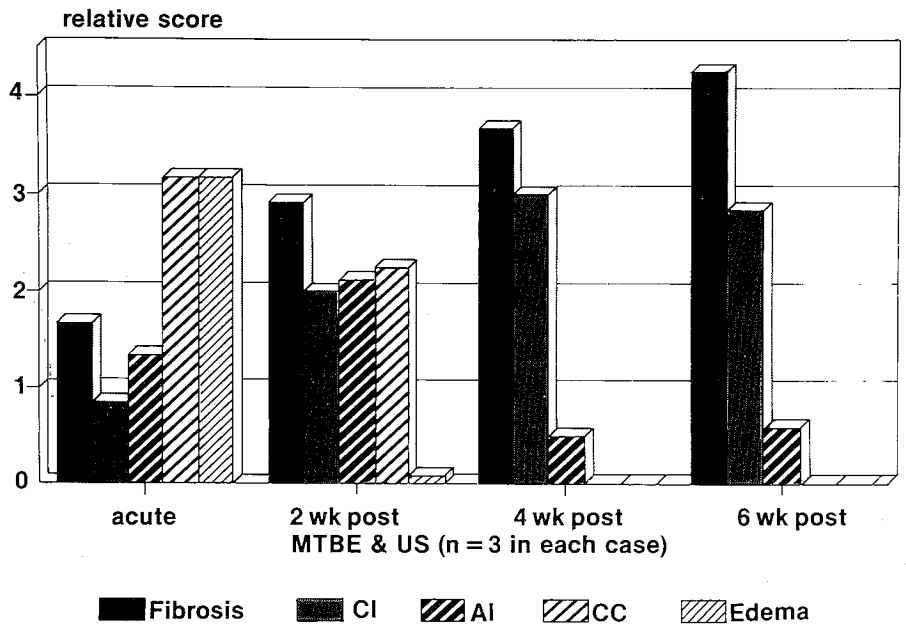


Fig. 4. Gallbladder pathology: MTBE plus ultrasound. Each grouping of bar graphs represents a different survival time of the pigs treated with MTBE and ultrasound. Each animal was scored in each category (fibrosis, CI = chronic inflammation, AI = acute inflammation, CC = coagulative changes, edema) on a scale of 0 to 5, with 5 being the highest. Each bar represents the mean value for each group.

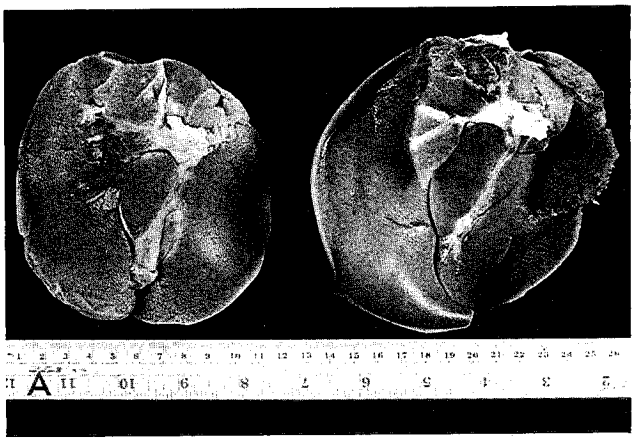
was 91.4% of an implanted mass of approximately 500 mg. This was achieved with a treatment time of 97.5 minutes. This is not only significantly faster than what we had earlier demonstrated using mono-octanoin and ultrasound, but it is also orders of magnitude faster than any reported studies using MTBE alone.[15,16] The emphasis of this research was to demonstrate the potentiating effects of ultrasound on MTBE. Further experimentation is necessary to establish the mechanism of action of this technology. Possibilities include a cavitational component, microacoustical streaming or stirring to remove unstirred layers, local temperature increase, or other mechanisms yet undefined.

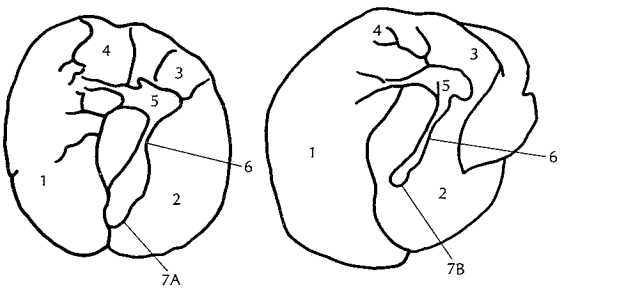
The pig experiments also allowed the evaluation of potential risks associated with this treatment when used in the prescribed manner. Although some elevations in serum enzyme levels were detected after the treatment, no major clinically significant elevations were seen. Furthermore, the elevated enzyme levels that did occur returned to pretreatment values after a recuperation period of four weeks or less.

Gross and histologic examination showed the most dramatic changes in the gallbladder. The fibrotic or ablated condition of the gallbladders, which developed during the posttreatment period, presumably rendered them dysfunctional or completely nonfunctional. The gross appearance of such a gallbladder is shown in Figure 5. Further experimentation is necessary to verify the ablative potential of this technology. In addition, the ability of this technology to selectively eliminate the gallstones while preserving the integrity of the gallbladder is an area of worthwhile research. If this separation of effects is achievable, it would present two options for treatment of biliary stone disease: either eliminate only the gallstones or simultaneously eliminate the gallstones and the potential source of the disease, the gallbladder itself. Becker and Kopecky[21] suggested that with a catheter in position within the gallbladder, a transcatheter gallbladder ablative procedure would be attractive to prevent recurrent cholecystolithiasis and that this ultimate goal could rival cholecystectomy in efficacy and surpass it in safety. Several investigators[22,26] have attempted to ablate the gallbladder percutaneously. The most recent experience reported by Becker et al.[25,26] suggests promising results from radiofrequency electrocoagulation of the cystic duct and sclerosing agents. The clinical usefulness or chronic complications of the percutaneous cholecystectomy presented in the current work, or its combination with ablation of the cystic duct, have yet to be realized.

When compared with other current methods for the elimination of gallstones, such as extracorporeal shock wave lithotripsy (ESWL) plus posttreatment adjunctive oral bile acids or continuous MTBE or mono-octanoin infusion, this proposed treatment modality offers several advantages. First, the data suggest that it is possible to render the patient completely stone-free in several hours or less. This is teleologically more attractive than the several months to a year necessary for the ESWL method or even the several days necessary for MTBE infusion. Second, this technique does not require more than several hours of patient exposure to MTBE. This not only eliminates the necessity for tedious infusion techniques, whether manually or by pump, but it also decreases the dosage of MTBE to which the patient is exposed. These factors tend to minimize any potential toxicity that may be attributable to MTBE itself. Indeed, this study's data suggest that adverse bioeffects are at a minimum.

The reduced treatment time, the minimal adverse bioeffects, and the potential for this technology to prevent recurrent disease should make this an appropriate method to add to the list of possibilities for the treatment of cholelithiasis.





B

visceral aspect

1. left medial lobe of liver
2. right medial lobe of liver
3. attachment surface of right lateral lobe
4. attachment surface of left lateral lobe
5. hepatic ducts
6. cystic duct
7A. gallbladder
7B. gallbladder remnant

Fig. 5. Pig gallbladder appearance after treatment with MTBE and ultrasound. (A) The visceral surface of two livers with attached gallbladder or gallbladder remnant. The gallbladder on the left was removed from a normal pig to which no therapy was given. The gallbladder shown on the right shows the effect of the combined treatment of ultrasound and MTBE after four weeks. (B) The areas of interest in the two tissue specimens. The most notable feature is the gallbladder remnant seen in the specimen on the right.

Acknowledgments

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