Review

Current Problem of Chemical Gallstone Dissolution

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Chemical gallstone dissolution is a mode of treatment that has been used for one entire decade, but still will evoke ardent discussions. How can we explain this phenomenon? The main reason is that there already had been a well established treatment of gallstone disease that is cholecystectomy. It is reliable and will bring relief soon. On the other hand chemical stone dissolution is considered as unreliable and time consuming, in many cases calling for surgery nevertheless, confronting the latter with an awkward situation since the slow process of dissolution had naturally favoured the development of complications. This way of arguing is purely emotional, unsustained by any facts.

Those who are seriously concerned with chemical gallstone dissolution will face different problems, e.g. has the safety of the administered drugs been thoroughly tested? Why will administration of chenic acid (CDCA) induce elevation of transaminases in 90% of patients treated? Will injury of hepatic tissue result? Are there disorders of fat metabolism, will bile salts favour the development of colo-rectal cancer and still worse could they prove teratogenic? Moreover, recently it could be shown that gallstones tend to calcify under urso acid (UDCA); will this factor reduce the value of chemical therapy? Another important problem is that of costs and benefits of conservative treatment, and for one decade the question is still unresolved what to do with pigment stones. The recurrence rate after stone dissolution has been already dealt with by Dr. Dowling, therefore it won't be mentioned again.

1. TOXICITY

a. Enzymes

As soon as in the early 1970's it was observed that about 30% of patients showed elevation of transaminases when treated with 15 mg CDCA/kg body weight. After reduction of dosage values returned to normal soon enough. We could see in our own collective that consisted of approx. 40 patients by then, that normalisation of transaminases occurred even if therapeutic dosage of chenic acid was continued.

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Even nowadays it is unknown what mechanism is responsible for elevation of transaminases. A distinct morphologic substrate for enzyme rise failed to be detected although simultaneous light- and electron optic investigations were minutely performed (12, 17, 36). But we have to concede that there are no investigations of liver histology covering samples before start of treatment, during and after transaminase elevation and that gallstone carriers even without cheno therapy will show in up to 50–60% unspecific histological alterations.

It was obvious to attribute the transaminase rise to the presence of monohydroxylated lithocholic acid (LC). Lithocholic acid is hepatotoxic in animal experiment (9, 20, 23, 31, 32, 37) and is formed from chenic acid by means of dehydroxilation. But Stiehl and co-workers (46) could show in 1974 that in man LC is being sulfated to approx. 70% and thus detoxified. We were able to corroborate this finding in animal experiments. Intravenous administration of non-sulfated LC induced considerable liver damage whereas the sulfated form proved to be really non toxic (19). Of course one could speculate that in man the toxic substrate could induce liver injury before being sulfated yet at present there is neither evidence nor counter-evidence for this hypothesis. Even that Stiehl and co-workers (45) proved unable to find a correlation between LC concentration but well between CDCA concentration in serum and rise of transaminases, does not definitely exclude LC as origin.

b. Liver structure

When chenic acid was fed to rhesus monkeys, severe morphologic injuries developed comparable to chronic hepatitis (9, 37, 52). This fact resulted first of all in the prohibition by law of chenic acid for the treatment of gallstone patients in England. But very soon thereafter it could be demonstrated that monkeys are incapable of sulfation (13) and experiments with monkeys are of no avail in this respect. When chenic acid was fed in various dosage to male and female Wistar rats there were only minimal changes by lightmicroscopy, electron-microscopically we could see development of vacuoles, proliferation of smooth endoplasmic reticulum, dilatation of bile capillaries and broadening of the so-called ectoplasm (20, 22, 23).

Our investigations aroused only little attention when published in the mid-seventies. People claimed that animal experiments could be but poorly transmitted to man, and especially not those with rats who would survive anything. It was this very fact and the knowledge that rats have an excellent system of detoxifying LCA by means of 6β - hydroxylation (14, 49) and therefore actually no alterations at all would have to be expected that attracted our attention. Applying an overdose of 1000 mg/kg body weight we could even kill the animals.

It is noteworthy that exactly the same alterations we have observed in animal experiments were seen 1982 during the NCGS (National Cooperative Gallstone Study) in 2 patients treated with chenodiol (11). All other findings such as round cell infiltrates, bile duct proliferation and central fatty degeneration are unspecific and cannot be discriminated from alterations in gallstone patients without treatment. Whether the morphologic alterations just men-
tioned are of any significance we don't know. Anyhow in patients on chenic acid treatment liver function should be monitored intervals yet not liver structure.

It is more or less unknown which influence cheno- or urso acid exert on a predamaged liver like e.g. in chronic active hepatitis and gallstones. We can merely contribute that we have treated 6 patients suffering from CAL with cheno- or urso acid without any evidence of deterioration of the basic disease as monitored by the usual laboratory data (24).

c. Diarrhea

When taking chenic acid transient diarrhea is a common feature that is rather welcomed by many patients and but occasionally calls for discontinuation of treatment. According to our current knowledge this diarrhea is caused by osmotically induced retention of water and sodium in the gut lumen and by simultaneously increased secretion in the sequel of a relaxation. But they may turn rather molesting and could contribute to discredit cAMP (7,51). The latter is a harmless and reversible disorder that is not related to the ulcerogenic effect of bile acids that had been described in animal experiments but is still controversial.

It is my opinion that those side effects due to cheno reported till now represent far more a molesting accompanying effect than a serious toxic reaction. But they may turn rather molesting and could contribute to discredit the treatment. Therefore we prefer treatment with ursodeoxycholic acid since transaminase elevations and diarrhea do occur really seldom in contrast to CDCA as can be seen in comparison of some 45 of our patients on cheno with some 85 patients on urso. Controlled investigations in Wistar rats have revealed furthermore that urso does not cause morphologic alterations of the liver (23).

The reason of this phenomenon is still unknown. Before it was presumed that UDCA is transformed to a lesser degree to LCA in the gut than CDCA (30, 42), but this could not be confirmed by recent investigations (4). Presumably the cause is the reduced treatment dosage of UDCA compared to CDCA and the reduced suppression of cholic acid synthesis in the liver. This results in a higher concentration of deoxycholic acid (DCA) in the gut lumen which will facilitate the excretion of LCA in feces. The cause of the rare incidence of diarrhea under UDCA is explained by the physical properties of this acid that tends to precipitate sooner in the gut than CDCA and thus loses its diarrhoeic effect (15, 48). By using UDCA instead of CDCA doctors and patients can be freed from anxiety of side-effects.

d. Fat metabolism

Coyne and co-workers have shown that CDCA inhibits HMG-CoA-reductase and cholesterol-7 alpha-hydroxylase in the liver (6). 7-alpha-hydroxylase is the key-enzyme of bile acid synthesis from cholesterol. When this enzyme is inhibited there is a risk of accumulating cholesterol in the organism. NCGS has demonstrated that 4.8% of the treated patients experience elevation of their serum cholesterol levels and this rise was seen exclusively in males and is caused by rise of the LDL-fraction (1). It is doubt-
ful whether this observation is of any importance especially as the cyto-
protective HDL-fraction remains unchanged. Nevertheless the authors con-
cluded that chenic acid should not be given to risk patients longer than for
24 months because of the possibility to favour coronary heart disease.

In the NCGS serum triglyceride levels fell dose-dependent in 57% of
the patients, yet rose again continuously till the 24th month of treatment
(43). If one wants to avoid such changes of the fat metabolism during chemical
stone dissolution, it is advisable to use UDCA instead of CDCA as drug. 10
studies have been reported on UDCA which payed attention to fat metabolism,
and no pathologic findings were detected.

e. Carcinogenicity

Since it has been discussed for many years that a meat-rich diet, bacterial
dehydroxylation of primary bile salts in the gut and especially DCA and LCA
show an cancerogenic or co-cancerogenic effect in animal experiments and
could favourably influence the development of colo-rectal cancer, naturally
this same question was discussed concerning bile salt treatment. In 1977 a
study was published by Reddy and Wynder (40) that in patients with large
bowel cancer the fecal concentration of DCA and LCA exceeded that one
of controls. A similarly minitious study by Moskovitz and co-workers dating
from 1979 (33) could not corroborate these observations, therefore we have
to await further studies. In rats rectal instillation of secondary bile acids and
bowl-specific cancerogens induced tumor growth, whereas up to now there
has been no successful tumor induction due to feed of primary or secondary
bile acids (34). Backed by numerous studies we can nowadays voice the opi-
nion that neither cheno- nor urso acid are, at least in therapeutic dose, a
cancerogen, procancerogen nor cocancerogen. Not even LCA is a carcinogen.
But since mutagenity tests (Ames) have revealed a mutagenic effect of LCA,
it could somehow be involved in tumor development (18).

But these studies need certainly not influence practical aspects of dissolu-
tion treatment because cheno- resp. urso acid is administered to patients only
in a dosage reduced by 70% and for only 1/3 of the time span compared
to the animal experiments. Yet dosage and time factor are of ultimate im-
portance for cancer development.

Last not least let me mention that any physician concerned with clinical
problems of gallstone therapy could be at a loss what to do now, as mean-
while there have been published 5 excellent studies, claiming that colo-rectal
cancer is increased after cholecystectomy and that tumor site has been shifted
to the right side. Thus e.g. in 1978 Capron et al. (5) found in 237 patients
with cancer 13% of cholecystectomized cases whereas in cancer-free patients
incidence of cholecystectomy amounted to only 3.3%. Peters and Keines (38)
found 5.4 % of cancer patients cholecystectomized, cancer developped one
decade sooner than in non-cholecystectomized and here too there was a shif-
ting to the right side. In the most recent study of Linos et al. (28) 2.4% of
operated women had colonic cancer which was significantly higher than in
the normal population.
2. STONE CALCIFICATION

1981 Bateson and colleagues (2) reported that under UDCA treatment primarily radiolucent stones were calcified after 6 to 12 months of therapy and thus resisted dissolution. Other authors confirmed these observations. In our own patients collective of approx. 180 patients of whom 140 were given UDCA, about 8% experienced calcification that could not be resolved by further administration of UDCA. There were speculations that calcification was induced by overdoses of UDCA because then the fraction of glyco-UDCA is augmented. G-UDCA is in contrast to tauro-UDCA poorly soluble and precipitates on the stone surface which in itself is said to facilitate the sedimentation of calcium-carbonate or phosphate. We could not confirm this observation in our patients since we have given to all a mean dosage of 11 mg/kg which corresponds to the optimal therapeutic dosage.

Furthermore it has to be clearly elucidated whether stone calcification is a sequel of UDCA at all. Thus e.g. NCGS could demonstrate that even with CDCA and placebo 7% of stone calcifications will occur (43); so perhaps calcification is just a normal process in the course of a gallstone. It could well be that use of the more polar substance TUDCA would counteract calcification (3).

3. BENEFITS AND COSTS

At present no discussion on chemical gallstone dissolution could possibly take place without the immediate argumentation that this method is compared to cholecystectomy, only suitable for a small number of all gallstone carriers, far more expensive than surgery and therefore absolutely useless. All of these statements are incorrect.

The benefits of a therapy can be determined by the total number of all patients having the disease in question, by the number of patients who are suitable for the therapy, and finally by a study of individual patients. With respect to the total number of all gallstone carriers the effective value of surgery is low; only 20% of all stone carriers undergo surgery in the course of their lives (27, 54) and only 0.5% each year (44). These figures reflect the current situation of gallstone surgery only in several European countries including West Germany. They do not give information on the number of suitable or unsuitable patients. A patient may be unsuitable for surgery owing, for example, to accompanying complications or to an unpronounced clinical picture. Since no precise numerical data are available on suitability, the benefits of surgery with respect to the number of suitable patients cannot be calculated. For suitable patients, however, the benefits of surgery are high: since the mortality is only 0.3-1.0%, success is relatively certain. Residual and recurrent stones decrease the success rate by about 10% (8, 10, 35). The benefits of conservative therapy in relation to the number of all stone carriers would, by comparison, be very great. Since only 15% (in the course of their lives) or 0.5% (annually) undergo surgery, 85% or 99.5% are available for stone dissolution — after subtracting all cases of asymptomatic stones a smaller, but probably still considerable, number. There is no uniform consensus of appraisal of the benefits of chemical therapy for the number of
all suitable patients and for the individual (21, 41, 43, 50).

In order to clarify the true benefits of conservative therapy we must ask ourselves: a) for how many of the 99.5% of all gallstone carriers who do not opt for surgery each year is drug therapy contraindicated and for how many is the therapy suitable? b) how high is the success rate for this group and for the individual patient? These can only be calculated approximately, since the number of asymptomatic stone carriers, as already mentioned, can at best only be estimated at present.

a) Lund in 1960 (29) and Wolpers in 1976 (53) showed that only 30% and 24% respectively of all patients examined would have been suitable for conservative therapy. Lund examined a collective that obviously had consulted a physician only at a late stage, since 70% revealed a gallbladder that was already a functional. Wolpers, in a retrospective study, examined cholecystectomy patients. Both groups were highly selective. In our prospective study, which was carried out with unselected patients of private physicians in the Rhein-Main area, 60% were suitable for stone dissolution and 40% had to be excluded (25). A comparison of the patients from the three studies showed that our patients consulted a physician at an early point when symptoms were not manifest, whereas especially in the Wolpers’ study they sought medical aid at a later point when complications were more frequent and surgery was indicated. The number of patients with symptomatic concrements who can be treated by drug therapy therefore depends on the stage of the disease. Since our collective had not been selected, it is at least representative for patients having symptomatic stones.

b) There is a wide discrepancy between the figures on the results of drug treatment. The underlying reasons are that in some studies insufficient doses or too short therapeutic periods were used (NCGS, SBGS, TCGS), that bile duct stones were not excluded with certainty, and that stones having a crescent-shaped calcium shell were also treated. Since 1973 we have treated more than 160 patients with 15 mg/kg CDC or 10 mg/kg UDC daily (26). In the selection of patients only stones larger than 2 cm, a nonfunctioning gallbladder, calcium containing stones or gallbladder stones concurrently with common duct stones were excluded. In all intermediate evaluations the treatment was ended in 60-70% of the cases with success (complete stone dissolution) and in 30-40% of the cases without success. The result was always checked by means of ultrasound and x-ray examination. The drop-out rate was 37.8% with the first 45 patients, which is in agreement with the literature (16, 39). After we had instituting a special consultation hour in 1975 during which patients were informed of success chances and risks in consultation with only one physician without the feeling being conveyed that they were merely subjects of a study, the drop-out figure fell to 2.8%. Side effects had little influence on the drop-out.

If we now compare the benefits of conservative therapy and surgery against the background of these figures, we arrive at the following conclusions for West Germany. Out of 60 million inhabitants, 12 million have gallstones (20%). Assuming that 40% of these are symptomatic concrements (4.8 million) and that 60% of these in turn are suitable for conservative therapy, there are 2.9 million patients who can be treated. In 1.73 million
patients (60%) the stones dissolve. 50% develop recurrent stones, so that with the average therapeutic period of 17 months in West Germany 865,000 patients are freed of stones by treatment with drugs or 610,000 per year. By comparison, 65,000 cholecystectomies are performed each year.

Let us take the extreme case in West Germany in which only 20% of all stone carriers can be considered for CDC or UDC therapy and 60% of this group are suitable. 30% of these will not take the medication or will decide in favour of surgery. The stones are successfully dissolved in 60% of the remaining patients, 70% of whom then develop recurrent calculi. This means that conservative therapy would still be beneficial for 1.1% of all stone carriers. As the current studies show, surgery benefits 0.5% of all stone carriers, whereby this figure is further diminished by the 10% residual and recurrent stones.

The question posed earlier can now be answered as follows:
1) The effectiveness of conservative therapy with reference to the total number of all stone carriers in West Germany is, under the most unfavorable conditions, at least twice as great as that of surgery (1.1%: 0.5%).
2) With reference to the number of suitable patients conservative therapy benefits 9% in the most unfavorable case and 21% in the most favorable case. It is not possible to determine a comparable figure for surgery, as the number of suitable patients is not known.
3) For the individual patient the benefits of surgery are 4.9 times higher than those of conservative therapy, if we subtract the mortality (1%) and the residual and recurrent stones (10%) from the total success rate for surgery and assume a success rate of 60% and a recurrence rate of 70% for drug therapy.

An important difference between chemical treatment and surgery is the patient number involved in each. To successfully treat 57,800 patients per year the surgeon must treat 1.1 times as many patients, the internist 4.7-7.9 times as many.

This extra expense, however, is not of significance for the expected costs. Extensive cost analyses, in which extra costs arising from complications of stone dissolution are added to the costs of conservative therapy, have shown that the costs for CDC therapy are equivalent to those for surgery (47).

In our calculation we have estimated the total costs of a chosen therapy as total amount of initial costs and expected costs. Expected costs are defined as expenses for one complication multiplied with the probability of its occurrence. By this balance we can construct a decision diagram that will produce a rather exact balance of costs.

Assuming a therapeutic success rate of 60% and a recurrence rate of 20%, conservative therapy costs 21,000 DM (including the extra surgical costs for the 40% of cases that resist therapy and for subsequent treatment of recurrent stones and their complications). A similar calculation for surgery yields a cost of 25,000 DM. If the success rate of chemical therapy drops to 20% or the recurrence rate rises to 70%, the calculated costs become 28,000 and 27,000 DM. These costs still lie below those for surgery, if we assume a mortality of 1.08% (29,000 DM).

Among the important factors in the cost calculation of conservative
therapy are the failure rate of 40-80% and the recurrence rate of 40-70%. These are the same factors that make it necessary to treat 4.7-7.9 as many patients with drugs if the same results as in surgery are to be achieved. In both calculations the same negative criteria were used. Thus the costs of treating 270,000 or 455,000 patients chemically correspond to those involved in the operation of 65,000 patients with a mortality of 0.5 or 1.08%. The reason for this result, which at first glance may seem astounding, are the lower costs for medication and the lack of a complication and mortality rate in stone dissolution. The costs for the uncomplicated surgical technique, on the other hand, rise drastically as a result of loss of working time, complications, pensions, and death.

If chemical stone dissolution were considered for all patients having symptomatic stones for which surgical intervention is not absolutely indicated, its benefits would be 2-10 times higher than those of surgery with the frequency in which it is currently applied in West Germany. With reference to all stone carriers, this would mean 1.1% for conservative treatment and 0.5% for surgery. With reference to all suitable patients conservative therapy would be of benefit to 9-21%. Comparative figures for surgery cannot be calculated. The individual patient, on the other hand, can only be told that the chance of his being permanently relieved of his concrements is five times greater with surgery than with conservative therapy, as long as the risk of recurrence is not reduced and the prediction of stone dissolution cannot be improved. The costs to the country for conservative and surgical therapy in terms are the same.

If conservative therapy proves unsuccessful, surgery with its low inherent risk can then be performed. Should surgery prove unsuccessful, conservative therapy can no longer be applied and the risks of a second surgical intervention are greater. If conservative therapy fails, only money will have been lost. Unsuccessful surgery, on the other hand, takes its toll in lost health and, in at least 3 out of 1000 cases, in lives. Thus the two therapeutic approaches have their advantages and disadvantages both in statistical and individual terms. If surgery is not explicitly indicated, the decision should be left to the patient.

4. PIGMENT STONES

I would like to conclude my presentation with that assessment of chemical gallstone dissolution. I just want to add one remark on pigment stones: for many patients with cholesterol gallstones in the gallbladder chemical therapy constitutes "Surgery to Swallow". But patients with pigment stones have to be asked to the operation theatre as before.
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