ACTA MÉDICA PORTUGUESA Vol. 4 n.º 1, 1983

THE UNITED STATES OF AMERICA NATIONAL COOPERATIVE GALLSTONE STUDY

The review article comparing and contrasting cheno and urso was written before the results of the US National Cooperative Gallstone Study (NCGS) were published.[1] The NCGS was the most ambitious and carefully designed study yet executed in the field of gallstones dissolution. For many, however, the results were disappointing and inevitably in a study costing almost 12 million US dollars, the publication of the principal findings has stimulated comment, controversy and concern. Already several provocative editorials have appeared in medical journals throughout the world[2-5] appraising the NCGS report, but in view of its importance, the Editor of **Acta Medica Portuguesa** suggested that a further comment on the American study, to complement the cheno-urso review, would be timely.

The NCGS was a multicentre, double-blind (or double-masked) trial involving 916 patients in which the safety and efficacy of chenodeoxycholic acid (CDCA or Chenodiol) were judged in three groups of patients randomly allocated to receive either placebo, low dose (375mg/day) or high dose (750mg/day) CDCA for 2 years.

Life table analyses showed that the efficacy of CDCA in producing complete gallstone dissolution* was 13,5% after 24 months treament with *high* dose CDCA, 5,2% with the *low* dose and 0,8% with placebo. The corresponding figures for partial (> 50% dissolution) plus complete gallstone dissolution were 40.8%, 23.6% and 11.0%. Patients compliance in taking the prescribed treatment was high — 93% *adherence* as judged by capsule counts at each visit. The dropout rate (patients defaulting from the trial) was low as was the withdrawal rate, by which the authors of the NCGS mean that physicians withdrew the patient and not that the patient withdrew from the study — a confusing nuance of distinction between withdrawal and dropout. The results of the study confirmed that efficacy, whether based on complete gallstone dissolution alone or on partial plus complete gallstone dissolution, was significantly greater in non-obese patient, in patients with buoyant stones and in patients with small stones. The conclusion about stone size was based on stone computed by *metrology* which unfortunanely, is impracticable in routine clinical use. Few family practitioners, for example, would be willing to calculate stone volume based on mathematical formulae. Fortunately, however, the cut-off point for stone volume corresponds to a maximum diameter of 17 mm, a figure remarkably close to the 15 mm limit noted by others.[9] Complete gallstone dissolution (but not partial plus complete gallstone dissolution) was seen significantly more frequently in patient whose pre-treatment fasting serum cholesterol was 227mg/dl. Partial plus complete gallstone dissolution (but not complete gallstone dissolutiom alone) occurred significantly more often in women than in men, in patient with *countable* stones and in whites than in non-whites. (One is concerned about possible selection/entry bias since there were only 16 non-whites compared with 289 whites in the high-dose group which is certainly not representative of the racial mix in the United States as a whole where approximately 20% of the population are non-whites).

One must also question the relevance of mathematically significant findings which apply only when the results of parcial **plus** complete gallstone dissolution are combined.
As regards safety, the NCGS again confirmed many *established* facts:

(1) dose-related hypertransaminasaemia which, in the NCGS, peaked at three months and declined thereafter despite continued treatment

(2) *clinically significant* (at least 2 episodes/month) diarrhoea in the high-dose group which, by cumulutive life table analysis, affected 40.9% of patients compared to 22.9% in the low dose and 25.9% in the placebo groups. The frequence of reported diarrhoea was not significantly different between the groups as a whole but was greater in the high dose group than in the other groups for women alone. Disappointingly, however, precise data on diarrhoea were available in only 289 of the 916 patients in the study.

(3) statistically significant reductions in fasting serum triglyceride levels which were greatest in the high-dose group, the nadir being at 9 months.

* confirmed by a second normal cholecystogram 3-4 months after the first, on-treatment xray had shown disappearance of the stones.

There were, however, two important observations which. although not totally original, may well be important:

(1) a significant increase in fasting serum cholesterol (mainly LDL) levels of approximately 20 mg/dl in both the low- and high-dose CDCA treated patients. Surprisingly, there was a corresponding increase of arround 10 mg/dl in the placebo group so that the increment in serum cholesterol attributable to the CDCA treatment alone, was in the order of 10 mg/dl — an increase of about 5% above the pre-treatment values. The significance of this finding is uncertain but if confirmed in long-term studies, it could, theoretically, increase the chances of coronary heart disease in patient treated to CDCA.
(2) *Clinically significant* hepatic abnormalities which led to termination of treatment in 8 of 305 patients in the high-dose (3% by table analysis), 1 of 306 (0.4%) in the low-dose, and 1 of 305 (0.4%) in the placebo group. In the patients given 750 mg CDCA/day, treatment was stopped in 7 because of *biochemical* abnormalities and in 1 because of liver biopsy changes.

So much for the facts — now for the opinions and for some views on the relevance of the NCGS report to the great mass of previously published results on clinical studies with CDCA and UDCA throughout the world.
The NCG study design was impeccable. The virtues of double-blind trials do not need extolling here. They are vitally important when subjective end-points, such as dyspeptic symptoms, are being assessed but arguably they are less important when objective end-points, such as confirmed complete gallstones dissolution or changes in the bile and blood chemistry, are being studied — provided of course that those carrying out the analyses are ignorant of the treatment. Furthermore, the major publication on efficacy and satefy[1] is only one of several publications by the NCGS which have already appeared.[6-8] Many important results from the ancilliary studies have yet to be published. These should prove invaluable to those working in the field and their *launch* in the medical press is eagerly awaited. Having said that, there are many criticisms which could be levelled at the NCGS. The cynical amongst us believed that the results in the main publication can be summarised as being too little, too few, too late, too short and too expensive:

Too little: Too little CDCA because, by most investigators standards, the doses of CDCA used in the NCGS were inadequate. The so-called *high* dose of 750 mg CDCA/day corresponds, on average, to 9.0 mg kg^{-1} day^{-1} in men and 10.6 mg kg^{-1} in women. Considering that the recommended dose of CDCA in non-obese is arround 13-15 mg CDCA kg^{-1} day^{-1}, the so-called low and high doses of cheno in the NGCS could more appropriately be classified as *very low* and *low*. Both are sub-optimal and in the opinion of the author this is likely to be main reason why the efficacy of CDCA in producing confirmed complete gallstone dissolution in the NCGS is disappointingly and unacceptably low.

It has been claimed that the main virtue of the NCGS report is to provide well controlled data on safety — but safety with a sub-optimal dose. The study was **not** designed to provide information about safety with 15 mg CDCA kg^{-1} day^{-1}. Arguably, therefore, the limited data about safety (and indeed about the efficacy of CDCA in desaturing bile and in dissolving gallstones) in the small number of *petite* women who, by virtue of being small and thin, took something approaching 15 mg CDCA kg^{-1} day^{-1} with the 750 mg dose, is of limited value.

Too few: Too few patients with confirmed complete gallstone dissolution. While no-one doubts the scientific contributions of the NCG study and conceptual brillance of its design, the *bottom line* for many doctors and most patients is *does it work*? With a maximum efficacy for confirmed complete gallstone dissolution of only 13.5% after two years treatment, the answer must be *yes — but not often enough.*

Too late: Too late because the results of the NCGS are no longer original. Most of the observations about the efficacy and safety of cheno have already been made and published from Europe, the United States and elsewhere — often 5 to 7 years before the NCGS results appeared.

One of the reasons for the delay lies in the long gestation period between conceiving the NCGS and extracting and publishing it — delays which are both inevitable and understandable.
It is an unfortunate fact of life that it takes a long time before the protocol for such large, government-funded multicentre studies, such as the NCGS, can be finalised with the results that when the findings are finally published, they may well be judged as being **passé.**
Indeed, the results of the NCGS may be too late for another reason.
In the opinion of many, cheno has already been superseded by urso as the medical treatment of choice for gallstone dissolution.[10]

Too short: Too short because no results are available for patients treated beyond 24 months. By this time, the final outcome of treatment was unknown in many cases. With longer treatment, would some of the nonresponders ultimately show gallstone dissolution? How many of the patients showing partial dissolution will end up with their stones completely dissolved? Unfortunately, the answer is — by no means all. Some may develop a non-functioning gallbladder which renders further medical treatment useless; some may develop other complications such as severe biliary colic, pancreatitis or obstructive jaundice requiring surgery; some may have non-cholesterol and, therefore non-dissolvable, stones or debris and some may default by completely withdrawing from the trial.
Ultimately, therefore, we need results such as those published by Maton et al[9], where there were only two possible final outcomes — either the stones dissolved completely (therapeutic success) or treatment stopped (failure).

Too expensive: It is not our business in Europe to pass judgement on size of the NCGS budget nor on how the US government financial *cake* for investigative medicine should be sliced. Such judgements have been made by our American colleagues, however, and many of them feel that the expense of huge collaborative studies, such as the NCGS and the National Cooperative Crohn's Disease Study are far from cost-effective
The NCGS report repays careful study but it is not for the casual browser. Although in general it is well written, it is not always easy to read. It is difficult, for example, to find out how many patients in the different treatment groups (rather than percentages of some unknown total) showed complete dissolution at the different times of the study. The actuarial life-table analysis provides a sophisticated method of estimating or percenting a result, after, say, 24 months treatment. The prediction is based on results in *all* patients starting treatment and allowance is made for the time during which they actually participated in the study. But it would also have been valuable to have had *hard data,* rather than projected figures and this is not always available. Perhaps this is an inevitable consequence of a study which had 10 administrative boards or comittees, 12 treatment centres, 5 central laboratories and 18 named authors.

CONCLUSIONS

Despite these criticisms, the NCGS report is the most important paper yet written about medical treatment of gallstones. Ironically, however, it has, at the same time, both helped and hindered the case for medical treatment of gallstones. Apart from the problems of bile acid dose and the inevitable inertia between conceiving a multi-centre study and having it approved and implanted, the NCGS has helped us by providing a standart of excellence in study design and a model of sophisticated analysis, which are unsurpassed. It may hinder us, however if the uninitiated believe (erroneously), that 13.5% complete gallstone dissolution is the maximum achievable efficacy after 2 years CDCA tretament.

Decisions by drug registration authorities about licencing CDCA in the US and elsewhere had been deferred until the results of this study were published. But with disappointing results, they could now be faced with a dilemma. They reasonably have expected a clear-cut set of recommendations about CDCA and guidance about whether or not it should be made available to doctors for prescription and to gallstone patients for treatment. In the event, they got neither.

Caution before authorising the *release* of new drugs is laudable but in the case of cheno, it now seems that more harm than good would be done by delaying its marketing further. It is to be hoped, therefore, that the results of NCGS will not be judged in isolation — rather that they will be considered in conjunction with the more optimistic findings from the large number of clinical studies published from Europe and elsewhere in the world.

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