A clinical and ultrastructural study of osteogenesis imperfecta after flavonoid (Catergen) therapy

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Summary

A trial of the flavonoid Catergen (Zyma) has been undertaken in 11 adults with osteogenesis imperfecta (OI).

The only significant clinical or metabolic side-effects were severe headaches, which necessitated the withdrawal of 3 patients from the trial. Patient compliance in terms of palatability of Catergen was good, and 3 of the 8 patients who completed the trial experienced subjective improvement.

After 6 months' treatment with Catergen, the abnormally narrow collagen fibrils found in the osteoid region in a pretreatment bone biopsy specimen from a middle-aged man with the common type 1 (autosomal dominant) form of OI showed a significant reversion to normal diameters. Post-treatment specimens from his 2 affected sons, who exhibited the same defect, showed a similar but less marked response.

Osteogenesis imperfecta (OI) is a well-known heterogeneous genetic bone dysplasia. Affected individuals often experience multiple fractures and in later life spinal malalignment and backache may result from progressive vertebral collapse.

At present, treatment is based upon orthopaedic measures and no effective medicinal therapy is available. Recent evidence indicates that the flavonoid group of drugs may have a beneficial effect in OI. A reduction in fracturing and histological, electron microscopic and biochemical evidence of improvement following treatment have been documented. The only significant clinical or metabolic side-effects were severe headaches, which necessitated the withdrawal of 3 patients from the trial. Patient compliance in terms of palatability of Catergen was good, and 3 of the 8 patients who completed the trial experienced subjective improvement.

We have undertaken clinical, biochemical and radiological studies on 11 patients treated for 6 months with the flavonoid Catergen (Zyma). These persons include a man and his sons with the common type 1 (autosomal dominant) form of OI in whom pretreatment studies of iliac crest biopsy specimens had revealed abnormally narrow collagen fibrils in the osteoid region. Our findings, including ultrastructural changes in bone biopsy specimens from these 3 patients after 6 months' Catergen treatment, are described and discussed in this paper.

Patients and methods

A group of 11 adult volunteers with OI participated in the trial after approval by the University of Cape Town Medical School Ethical Committee.

After explanation of the investigation procedure, informed consent was obtained. Clinical examination, urinalysis and routine haematological tests were undertaken and 12-channel serum analysis, including calcium, phosphate and alkaline phosphatase estimations, was carried out. In order to provide a bone density baseline, radiographs of hands and femoral shafts were used for measurement of ratios of the cortex and medulla, and computed tomography (CT) of the fourth vertebral lumbar body was undertaken in 3 cases. Finally, iliac crest biopsy specimens were obtained from a 55-year-old White man and 2 of his sons (aged 18 and 21 years) with type 1 (autosomal dominant) OI for electron microscopic appraisal of bone ultrastructure. Age-matched control specimens were obtained from a volunteer (P.B.) and from unaffected persons undergoing iliac crest biopsy during investigation for suspected haematological disease.

After the preliminary evaluation had been completed, Catergen tablets (500 mg 3 times daily) were prescribed. Thereafter the patients were seen at monthly intervals and arrangements were made to enable them to contact the investigators for immediate reappraisal if any untoward symptoms occurred. After treatment for 6 months, note was taken of any apparent benefit in terms of lessening of bone pain, fracturing tendency and vertebral body collapse, bone density was reassessed, and the biochemical and haematological analyses were repeated. Repeat biopsies of the iliac crests of the father and his sons with type 1 OI were performed and the bone specimens were processed and analysed as previously described. The Mann-Whitney U test was used to determine whether there was any change in the collagen fibril diameter distribution before and after treatment.

Results

General outcome

Of the 11 subjects who commenced the trial, 3 were withdrawn because of severe headaches attributable to the treatment. The 8 who completed the course of therapy did not have any untoward reactions and their routine biochemical and haematological parameters remained essentially normal throughout.

Subjective results

Of the 8 subjects who completed the trial, 1 male was adamant that his backache (ascribed to vertebral collapse) had improved. Two adult females also considered that they had experienced remissions of backache and pain at the fracture sites. The other 5 had noticed no change in their condition.
Objective results

Biochemical parameters of bone metabolism and radiographic measurements of skeletal density in terms of ratios of cortex and medulla in the metacarpals and femora of all 8 subjects who completed the trial were unchanged by the course of treatment. In addition, the relative densities of the fourth lumbar vertebral bodies and surrounding tissues, as measured by CT scans in 3 cases, were unaltered by the therapy. Since these observations are non-contributory, no further details will be presented.

The most significant finding was a reversion to normal on electron microscopy of the post-treatment bone biopsy specimen from the 55-year-old man. In contrast to the narrow, spindle-shaped, inactive osteoblasts found in the first specimen, these cells were plump and filled with dilated cisternae of rough endoplasmic reticulum, suggesting active collagen synthesis (Figs 1 and 2). The collagen fibrils closest to the cells were narrow in diameter, whereas those distal to the osteoblasts attained normal diameters. Analysis of fibril diameter using the Magiscan system of automatic quantitative image analysis showed a marked shift to the right, with peaks at 0.04 - 0.08 μm compared with 0.03 - 0.06 μm before treatment (Fig. 3).

Discussion

The main clinical problems in OI are multiple fractures of the long bones in childhood and progressive collapse of the vertebral bodies in adulthood. These complications are very variable, but some affected persons are severely handicapped. At present treatment is largely orthopaedic and no medicinal therapy is available. Various preparations have been tried, including calcium, calciferol and anabolic steroids, but no consistent benefit has been observed.

Catergen ((+)-catechin, (+)-cyanidanol-3) is a flavonoid which has been widely used in the treatment of chronic hepatic disease. It is generally regarded as being relatively innocuous, and side-effects are few. None of our patients found it to be unpalatable, but 3 were withdrawn from the trial when severe headaches developed. The headaches disappeared within 24 hours of withdrawal of the Catergen in 1 of these subjects, but the pain returned when therapy was
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The pathogenesis of these spinal changes is uncertain, but osteoporosis, microfractures or both have been incriminated. Vertebral involvement is very variable, and some individuals with OE are severely affected while in others the spine is normal. This problem is compounded by the heterogeneity in OE, and for these reasons the assessment of symptomatic response in adulthood is very difficult. Nevertheless, it is possible that the main therapeutic application of Catergen in adults with OE will be for vertebral collapse and spinal pain.

Routine biochemical and haematological parameters remained normal throughout the trial, as did the results of urinalysis. Furthermore, measurements of cortical/medullary ratios in metacarpals and femora and CT scans of vertebral bodies revealed no evidence of a positive bone response. The demonstration of a reversal towards normality at the ultra-structural level in the 55-year-old man seems to be a genuine pointer to the activity of Catergen. However, it is impossible to draw firm conclusions from a single case, and more age- and site-specific data are required to elucidate the true significance of these observations. It is also impossible to be certain whether the histological improvement represents an alteration in the progression of the disease, but it is noteworthy that this patient was adamant that his longstanding backache had re-

There have been several reports indicating that Catergen may affect collagen biosynthesis in various ways. These include an increase in cross-link formation in normal and lathyritic collagen, a reduction in prolyl hydroxylase and lysyl hydroxylase activity, and an accelerated conversion of soluble to insoluble collagen in lathyritic, diabetic and genetically abnormal collagen. Collagen synthesized in the presence of Catergen has been shown to be more resistant than normal to the action of collagenase and pepsin digestion, and collagen biosynthesis has variously been reported to be decreased, unaffected and, in the case of adjunt arthritis, increased. Several of these properties may be relevant to the amelioration of the collagen defects in OE: for instance Catergen may, by its action on lysyl hydroxylase activity, reduce the increased level of hydroxylsine reported in the collagen of many patients with type 1 OE; or it may, by increasing the number of cross-links (which may be deficient or exhibit delayed maturation in OE), improve the supralower and stability of the collagen fibres and, since collagen biosynthesis is reduced in OE both in culture and in tissues, it may act to stimulate collagen production, as in adjuvant arthritis.

It has been claimed that the drug does not alter already synthesized collagen but acts only on new collagen. A greater turnover in collagen production would be expected in younger men, and for this reason the lack of a positive response in the affected sons compared with their father is paradoxical. It may be that detection of improvement in collagen fibril diameter is independent on the inclusion in the sample of a new or recent bone deposition site, which would fit the appearance of the osteoblasts in the older subject. The apparent absence of a response in the sons may therefore be a sampling phenomenon due to the small area of bone examined. It is also possible that the metabolism of Catergen may be different in the younger men or that the sons had been less meticulous than their father as regards regular ingestion of the tablets.

Since OE is very heterogeneous, it is possible that Catergen will be effective only in some forms of the disorder. However, an improvement in collagen morphology in a group of children between 4 and 12 years of age with various forms of OE has been described, so it appears that the range of potential activity within the diagnostic category of OE may be fairly wide. At this stage, however, delineation of the various types of OE is very imprecise and it is impossible to reach firm conclusions concerning therapeutic application. We recognize that our sample is small and that our findings require confirmation from a larger series. However, in view of the comparative rarity of OE and the difficulty in obtaining bone biopsy specimens, we believe that these encouraging preliminary observations should be brought to the attention of colleagues working in this field.

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REFERENCES

Management of patients with a diastolic blood pressure of 90 mmHg in the third trimester of pregnancy

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Summary
A retrospective study of 50 patients admitted to the Peninsula Maternity Hospital, Cape Town, with a diastolic blood pressure of 90 mmHg was carried out. Proteinuria and a serum urate level of 0.36 mmol/l or more were found to be risk factors in this group. It is suggested that these patients can be managed as outpatients if no proteinuria is present and the serum urate level is less than 0.36 mmol/l; they should be trained to test urine at home and should be followed up on a weekly basis. A small prospective study showed that home urine testing was both workable and satisfactory.

Management is one of the commonest complications of pregnancy and is the commonest cause of maternal death in the UK. Proteinuric hypertension is also the commonest cause of maternal death in Cape Town. Hypertension developing in an otherwise normotensive, non-proteinuric woman is termed pregnancy-induced hypertension (PIH). PIH can be classified into three groups: (i) gestational hypertension; (ii) pre-eclampsia (with proteinuria); and (iii) eclampsia (with eclamptic fit).

The patient arriving at a busy antenatal clinic with a diastolic blood pressure of 90 mmHg often presents a management problem. Is she to be admitted to hospital or followed up as an outpatient? How often should she be seen and what investigations should be done? With pressure on the limited antenatal beds, these questions become particularly relevant.

Patients and methods
A retrospective study of patients seen over a 6-month period was carried out at the Peninsula Maternity Hospital, Cape Town. During this period all patients with a diastolic blood pressure of 90 mmHg were admitted to the antenatal ward for assessment. All those in the third trimester of pregnancy and with a diastolic blood pressure of 90 mmHg on admission were included in the study (patients with essential hypertension were excluded).

All patients were kept in hospital for at least 48 hours for bed rest, determination of the blood biochemical values, urinalysis, and 6-hourly blood pressure recordings. Fifty patients met the criteria for inclusion in the study and were placed in one of four groups: group A — no proteinuria, blood pressure settled in 48 hours, no recurrence (17 patients); group B — no proteinuria, blood pressure settled in 48 hours but subsequently rose again (20 patients); group C — no proteinuria, blood pressure did not settle in 48 hours (4 patients); and group D — proteinuria present (9 patients). Age, parity...