Calcium metabolism in bone disease: effects of treatment with microcrystalline calcium hydroxyapatite compound and dihydrotachysterol[1]

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Summary: Microcrystalline calcium hydroxyapatite compound (MCHC) was given orally together with small doses of dihydrotachysterol (DHT) to a number of patients with osteogenesis imperfecta (OI). Serial calcium and phosphate balances in three patients representing wide variations in severity of OI are presented over periods from eight months to two years. The combination of MCHC and DHT resulted in an immediate positive calcium balance which was maintained throughout the period of assessment in 2 cases. However, no radiological improvement could be demonstrated. Substituting calcium gluconate for MCHC resulted in a reduction of positive balance. No adverse effects were noted. The reasons why MCHC with DHT should result in increased calcium retention are discussed. This combination of MCHC and DHT could be of benefit in many common situations of bone demineralization, such as osteoporosis.

Introduction

There are many disease states in which bones are poorly mineralized. When there is a true deficiency of uptake, these changes can often be reversed by oral supplements of soluble calcium salts and vitamin D preparations. However, there are a number of bone diseases, such as osteoporosis, in which it is possible that increased calcium uptake might be of therapeutic benefit even though no clear biochemical abnormality has yet been found. In these situations, oral supplements of soluble calcium salts and vitamin D preparations usually fail to produce a marked increase in overall calcium balance because of poor absorption.

Microcrystalline calcium hydroxyapatite compound (MCHC; Ossopan) is a naturally derived calcium extract of bone. As well as calcium and phosphate, MCHC contains many other minerals in approximately physiological proportions together with various other organic constituents of bone. Evidence that MCHC is better absorbed than other calcium supplements (Windsor *et al.* 1973) has led to various clinical applications. Reports have suggested that oral MCHC can accelerate fracture healing (Frank & Heppner 1953, Mills *et al.* 1965), and improve or prevent osteoporosis (Nilsen *et al.* 1978, Brenton & Dent 1976).

The syndrome known as osteogenesis imperfecta (OI) represents a group of inherited disorders of varying severity which predominantly affect bones, but in which there are also abnormalities of other mesenchymal tissues. Frequent bone fractures occur, which are often slow to heal. Since there is not normally any biochemical abnormality, a primary defect of bone mineralization is considered unlikely. However, disuse osteoporosis is very frequently seen as a further complication in this crippling disease.

Since both the slowly healing fractures and the osteoporosis of OI could theoretically benefit, we have given MCHC together with dihydrotachysterol (DHT) in small doses to a number of patients with this disease. Assessment of clinical response is of necessity long-term,

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but we are at this time able to report the effects of treatment on calcium balance in three patients with OI of widely differing severity.

Patients

Details of the three patients are summarized in Table 1. Patient 1 had very severe and incapacitating disease, with frequent chest infections associated with gross kyphoscoliosis; patient 3 had only mild disease; and patient 2 had disease of intermediate severity. Plasma calcium and phosphate levels were normal in all three patients.

Radiological examination in patients 1 and 2 showed evidence of multiple fractures at varying stages of healing, together with widespread abnormalities of bone; all long bones were slender with thin cortices and the leg bones were frankly osteoporotic in both cases. Radiographs from patient 3 were essentially normal, apart from the old fractures.

Table 1. Details of patients

	Patient 1	Patient 2	Patient 3
Age at start of study (years)	13	13	4
Sex	F	F	M
Weight (kg)	13	30	15.6
Blue sclera	No	Yes	Yes
Family history of OI	No	Yes	Yes
Age first fracture sustained (years)	Neonatal	2	1½
Mobility	Wheelchair	Calipers	Normal
Below 50th percentile height	Yes	Yes	No
Initial serum biochemistry:			
Calcium (mmol/l)●	2.5	2.3	2.5
Phosphate (mmol/l)■	1.4	1.3	1.5
Alkaline phosphatase (K-A units)	15	11	23

● Serum calcium: 1 mmol/l ≃ 4.0 mg/100 ml
■ Serum phosphate: 1 mmol/l ≃ 3.1 mg/100 ml

Methods

The parents of all three patients were fully informed as to the nature of this trial and gave consent for their children to be included.

Calcium and phosphorus balance studies were performed in a specialized metabolic ward, using standard methods, with cuprous thiocyanate as a continuous internal marker. Balances were calculated over four-day periods.

Initially, baseline balance studies were performed for eight days. Oral MCHC in a dose of 8 g/day was then started and the balance studies continued. After an average of sixteen days treatment with MCHC, oral DHT was added, in a small weight-related dose (0.1–0.25 mg/day) and the balance studies continued for approximately sixteen further days. The patients were then discharged from hospital continuing to take MCHC and DHT.

Five months later, the patients were re-admitted for a further period of calcium balance assessment. Patients 1 and 2 were studied for eight-day periods to assess the effect of prolonged treatment. In the case of patient 3, after eight days of balance studies MCHC was stopped and the equivalent dose (18.3 g/day) of soluble calcium gluconate (Sandocal) substituted. After a further sixteen days of balance studies the patient reverted to MCHC and was discharged taking this and DHT.

Patients 2 and 3 were subsequently readmitted for further eight-day balance studies, patient 2 after eight months and patient 3 on three occasions separated by intervals of two, four and ten months respectively. Patient 1 died before a third study could be performed. Treatment regimes are summarized in Figures 1, 2 and 3.

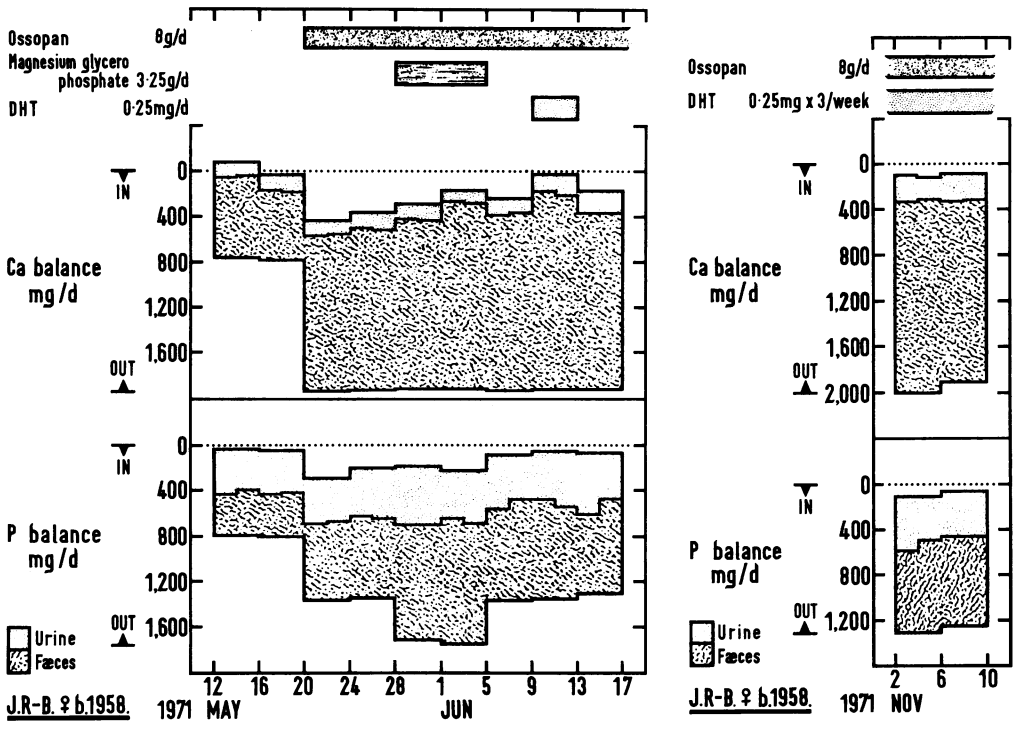

Figure 1. Calcium and phosphorus balances in patient 1

Results

No new symptoms or signs of disease, nor any new fractures, occurred during the period of the study. Patient 1 died as a result of one of her many respiratory infections after some six months treatment with MCHC. No features suggestive of adverse reactions to treatment were noted.

Calcium and phosphorus balances are shown in Figures 1, 2 and 3. Patients 1 and 2 had near-zero baseline calcium balances which immediately became significantly positive when MCHC was started. This initial dramatically positive balance gradually decreased until DHT was added, when balances again became very positive. This positive balance was still maintained after six and fourteen months in patients 1 and 2 respectively, although the positive balance was quite small in patient 1. In patient 3, there was a small positive baseline calcium balance which was not initially affected by MCHC. However, when DHT was added, the balance became much more positive and remained so for the further two years of assessment. Changing from MCHC to calcium gluconate resulted in a sudden marked reduction in both calcium and phosphorus balance.

Discussion

Our results demonstrate that treatment with MCHC and small doses of DHT results in an immediate positive calcium balance which appears to be sustained for long periods of continuing treatment, thus confirming previous reports that the minerals in this product are available for absorption (Windsor *et al.* 1973, Dent & Stamp 1971). We have also confirmed in one case the superiority of this treatment over soluble supplements such as calcium gluconate.

The balance data presented must be interpreted with reference to body size. In particular, the apparently small positive balances in patient 1 are probably very significant in terms of her

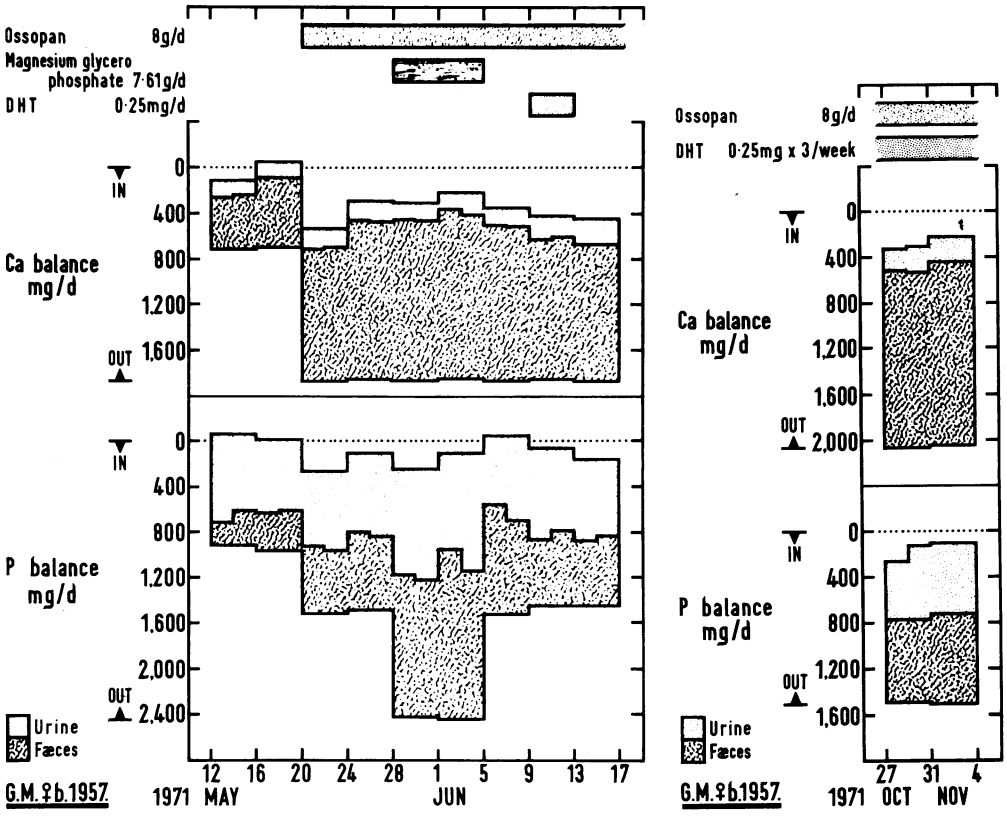

Figure 2. Calcium and phosphorus balances in patient 2

body weight of only 13 kg. The balances achieved could well be the maximal attainable in a patient of this size.

It would seem that the prolonged calcium balances apparently produced in these patients should have resulted in increased bone density clearly visible radiologically. Thus patient 3 apparently had a positive calcium balance of 400 mg per day for two years representing a gain of 290 g of calcium. Since a normal adult skeleton contains only 1 kg of calcium, and these children's skeletons obviously contained very much less, such a gain should have been demonstrable. Unfortunately it has not proved possible in any of these patients to demonstrate radiological improvement, perhaps because of factors such as healing fractures, body growth and immobility at certain times.

The fact that the combination of MCHC and DHT can produce a positive calcium balance is obviously only suggestive of possible therapeutic benefit. The true test of treatment must be its ability to improve bone strength, reduce the number of fractures and perhaps facilitate healing of those fractures which do occur. Such information will only be available when long-term prospective studies have been completed.

The possible implications of our findings are of widespread importance. OI is certainly a crippling disease for which any effective treatment would be welcomed, but it is undoubtedly rare. On the other hand, there are many common diseases involving demineralization and weakening of bone in which increased calcium uptake could be beneficial. It has already been reported that MCHC can help back pain in postmenopausal osteoporosis (Durance *et al.* 1973), give protection against osteoporosis in patients treated with corticosteroids (Nilsen *et al.* 1978), and be beneficial in idiopathic juvenile osteoporosis (Brenton & Dent 1976). If the

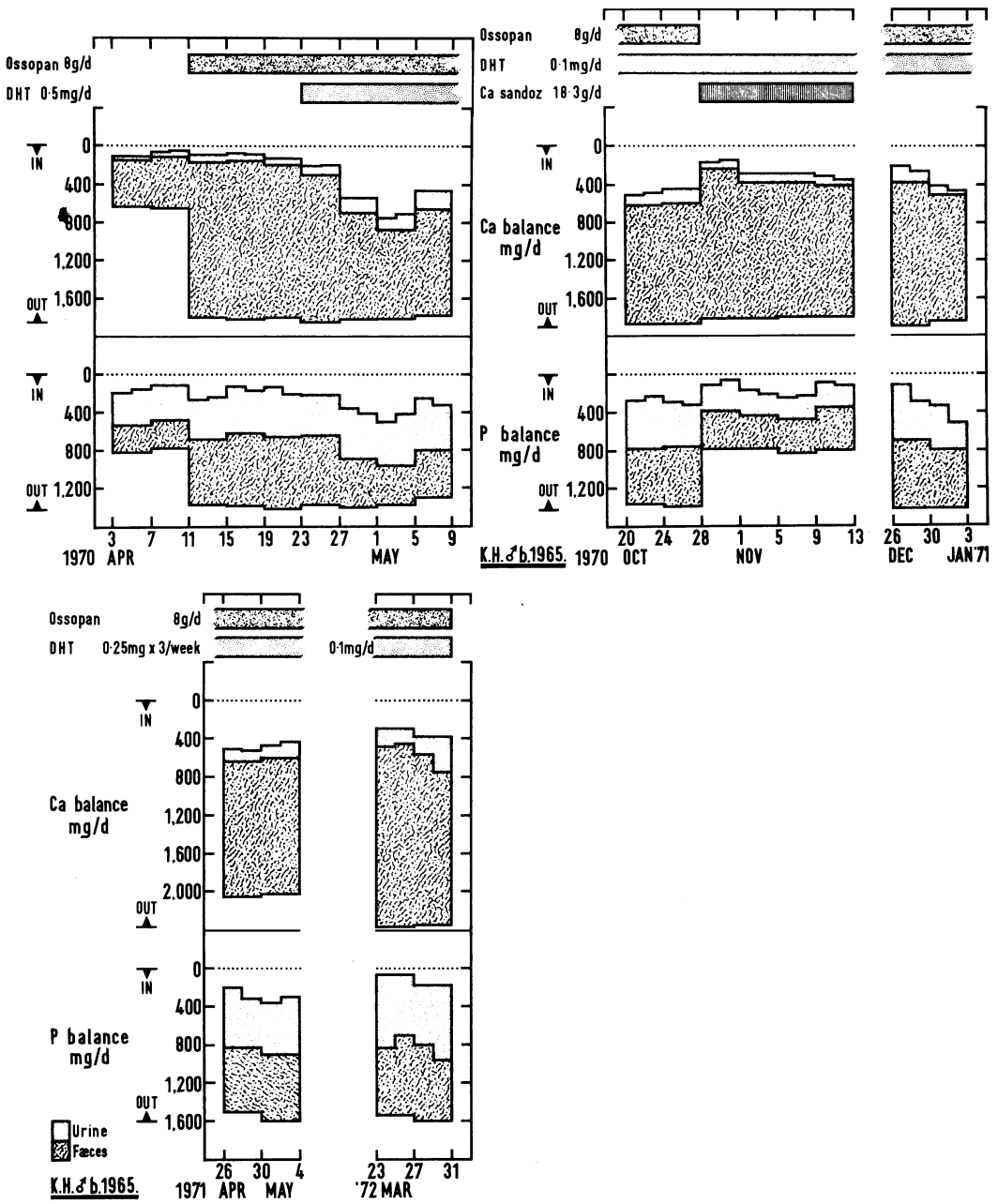

Figure 3. Calcium and phosphorus balances in patient 3

efficacy of MCHC and DHT in these situations can be confirmed, this could be of considerable therapeutic importance.

There has been considerable speculation as to why an essentially insoluble calcium preparation should be more readily absorbed than the soluble alternatives. Küng (1948) postulated that it is more readily handled by the intestinal mucosa, and it has been long known that the presence of amino acids or their residues can enhance calcium absorption

(McCance *et al.* 1942). Windsor *et al.* (1973) have shown that treatment with MCHC increases uptake of simultaneously administered labelled calcium, indicating that the increased absorption does not apply only to the MCHC itself.

In relation to OI, it is possible that some of the mineral or organic constituents of MCHC apart from calcium may be important. However, improved bone mineralization is likely to be beneficial and a positive calcium balance is an essential first step to remineralization. Furthermore, when fractures do occur MCHC may well accelerate their healing (Frank & Heppner 1953, Mills *et al.* 1965).

MCHC is well tolerated, even by small children, and does not appear to result in any undesired effects. The absence of hypercalcaemia or hypercalciuria have already been noted by Nilsen *et al.* (1978).

In summary, the combination of MCHC with small doses of DHT can be shown to result in a positive calcium balance. MCHC has been reported to be beneficial not only in OI but also in common situations of bone demineralization such as osteoporosis. If remineralization of bone in such situations can be demonstrated, MCHC may well have widespread potential applications for the treatment of bone diseases.

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