Possible prevention and treatment of steroid-induced osteoporosis

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Summary
Patients with steroid-induced, juvenile and senile osteoporosis were studied using balance techniques.

The changes in calcium and phosphorus balance associated with glucocorticoid therapy were corrected with vitamin D and bendrofluazide given in combination. No hypercalcaemia occurred in osteoporotic patients who continued to receive glucocorticoids. Calcium and phosphorus balance was also improved in the osteoporotic subjects not receiving steroids, but these patients became hypercalcaemic during treatment.

It is suggested that vitamin D, bendrofluazide and steroids antagonize the actions of one another on the renal tubule, gut and bone and in this way prevent the increased calcium which occurs with glucocorticoid therapy. Since the increased calcium and negative calcium balance induced by glucocorticoids is considered to be the result of excessive bone resorption, an adequate dose of bendrofluazide and vitamin D in combination might prevent the development of, or even reverse, steroid-induced osteoporosis.

Introduction
Theoretically, osteoporosis may represent an imbalance of factors which affect the formation and resorption of bone (Pak and Bartter, 1972). In man, glucocorticoid-induced osteoporosis is usually considered to be the result of increased bone resorption (Jowsey et al., 1965; Gallagher et al., 1973; Wajchenberg et al., 1969), although decreased bone formation may also contribute to some extent (Riggs, Jowsey and Kelly, 1966).

A rise in urinary calcium and a negative calcium balance usually develops in patients given large doses of glucocorticoids, and since these drugs inhibit intestinal absorption of calcium in animals and man (Stoerk and Arison, 1961; Collins, Garrett and Johnston, 1962; Bunim et al., 1958; Slater et al., 1959; Nordin et al., 1968; Gallagher et al., 1973) the increased urinary calcium is generally considered to be the result of excessive bone resorption.

It would, therefore, be reasonable to assume that if the increased calciuria and negative calcium balance induced by glucocorticoids were reversed, the development of osteoporosis might be prevented or modified.

The authors have been able to correct the changes in calcium and phosphorus balance associated with glucocorticoid therapy, by the use of a simple regime which was also given to two osteoporotic patients who were not receiving glucocorticoids. Calcium and phosphorus balance studies are reported in these five individuals. The possibility that the drugs used may be of therapeutic benefit in glucocorticoid-induced and possible other forms of osteoporosis is discussed.

Methods
Balance study techniques and phosphate analysis have been previously reported (Walker and Collins, 1965). Balance periods were 6 days in patients 1, 2, and 3; and 4 days in patients 4 and 5. Carmine dye was used as a period marker. Faecal calcium and phosphorus values were corrected for barium sulphate or copper thiocyanate, one of which was used as a continuous faecal marker. Faecal barium was estimated by atomic absorption spectrophotometry and faecal copper by the method of Dick (1969).

Urinary inorganic phosphate was estimated on all urine samples using the autoanlyser method N4b (Technicon Autoanlyser Handbook). Calcium analysis was performed by atomic absorption spectrophotometry on the Unicam SP 96 model using Unicam atomic absorption method Ca2.
Results

Balance studies are represented graphically in Fig. 1.

Case 1

A 36-year-old man with rheumatoid arthritis who developed hypercalciuria and a negative calcium balance when given prednisolone 20 mg daily. Calciferol 0.5 mg/day and bendrofluazide 5 mg/day was given and the patient taken off balance. The patient was 'rebalanced' eighteen days later. Hypercalciuria had been controlled and a positive calcium balance induced by therapy. There was no rise in plasma calcium which remained between 8.9 and 9.6 mg/100 ml during therapy.

Case 2

A man who had been treated for severe asthma with prednisolone 20–30 mg/day for 6 years. The patient had lost 2 inches in height and had severe back pain. Radiological examination of the spine revealed osteoporosis with collapse of L3 L4 vertebrae. Balance studies showed the patient to be in negative calcium balance and when given 1 mg of calciferol daily urine calcium increased and faecal calcium fell. Calcium balance remained virtually unaltered until bendrofluazide 5 mg daily was added to the regime. This caused a fall in urine calcium and calcium balance became zero. When the bendrofluazide was started, the dose of calciferol was reduced to 0.5 mg daily. This reduction in vitamin D

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**FIG. 1.** Calcium and phosphorus balance studies in patients given prednisolone (patients 1–3) and not given prednisolone (patients 4–5) treated with bendrofluazide and vitamin D. DHT = dihydrotachysterol.
Steroid-induced osteoporosis

dosage caused a further rise in faecal calcium and the
development of a negative calcium and phosphorus
balance. Urine calcium remained well within normal
limits.

Treatment was continued with 0.75 mg of cal-
ciferol and 5 mg of bendrofluazide in addition to
prednisolone. There was relief of back pain within
6 months and there was no further loss of height
over 18 months. The calcium balances were not
repeated during this period of time.

Case 3

A 62-year-old woman with rheumatoid arthritis
had been treated with prednisolone 7–15 mg/day for
8 years. On admission for balance studies the patient
was receiving 7.5 mg/day of prednisolone and this
was increased to 15 mg/day. The patient was
balanced and at the beginning of the third period
calciferol and bendrofluazide were begun. There was
no significant change in her calcium balance or urine
and faecal calcium over the next 24 days. It is
realized, in retrospect, that longer balances with a
higher dosage of vitamin D were necessary to induce
a positive calcium balance.

Case 4

An 11-year-old male with juvenile osteoporosis,
whose calcium balance improved markedly to
+440 mg with dihydrotachysterol (DHT) and
bendrofluazide. Hypercalcaemia developed after
16 days of treatment which was discontinued.

Case 5

A 68-year-old man with senile osteoporosis.
Treatment with 1 mg/day of DHT and bendroflu-
azide resulted in a marked improvement of calcium
balance. Treatment was discontinued because
hypercalcaemia developed, despite the reduction of
DHT to 0.5 mg/day.

Discussion

Hypercalciuria and a negative calcium balance
invariably develop in patients given very large doses
of glucocorticoids. This effect is probably dose-
dependent (Pechet, Bowers and Bartter, 1959;
Geschwind, 1961; Eisenberg, 1966; Wajchenberg
et al., 1969) and due to defective intestinal and renal
tubular resorption of calcium (Pechet et al., 1959;
Gallagher et al., 1973).

The authors have improved calcium balance by
using a combination of drugs the individual actions
of which are well known. Vitamin D increases
intestinal absorption of calcium and faecal calcium
falls. The compound would thus be expected to
correct the intestinal defect of calcium absorption
due to glucocorticoids and this appears to be the
case (Nordin, 1973). Although administration of

vitamin D and of glucocorticoids results in increased
calciuria, it does so by different mechanisms. Large
doses of glucocorticoids raise urinary calcium by
inhibiting renal tubular resorption of the ion (Pechet
et al., 1959) whereas, in the presence of normal
parathyroid glands, vitamin D probably increases
renal tubular resorption of calcium (Gran, 1960;
Nordin, 1973) causing an increase in plasma calcium
with resultant hypercalciuria. Vitamin D and gluc-
ocorticoids, therefore, have opposite actions on the
renal tubule and would be expected to counteract
each other.

Both glucocorticoids (Jowsey et al., 1965;
Gallagher et al., 1973) and vitamin D increase bone
resorption. In the case of glucocorticoids there are
two possible mechanisms by which this may occur; it
may be secondary to a prolonged negative calcium
balance caused by the action of glucocorticoids on
the gut and renal tubule and in support of this
osteoporosis can be induced in animals by a calcium
deficient diet (Crawford et al., 1957; Harrison and
On the other hand, increased bone resorption may
be due to a direct action of glucocorticoids on bone.
There is in fact evidence which points to the reverse;
namely, that glucocorticoids actually inhibit bone
resorption (Raisz et al., 1972; Nisbet and Nordin,
1969). Indeed, although the exact mechanism of
action is unclear, many patients with malignant
hypercalcaemia and vitamin D overdose (Myers,
1962; Verner, Engel and McPherson, 1958), two
disorders in which bone resorption may be high,
respond to glucocorticoid therapy by normalization
of serum calcium.

Thus, the negative calcium balance induced by
large doses of glucocorticoids acting on the gut and
kidney might cause increased mobilization of bone
and overshadow any direct inhibitory effect of
glucocorticoids. Such a direct inhibitory action of
glucocorticoids on bone resorption may thus be
unrecognized and only be detectable with small doses
of the compound, larger quantities of glucocorticoids
increasing bone resorption through the mechanism
of a negative calcium balance.

If this negative calcium balance effect of gluco-
corticoids were corrected, the direct inhibitory effect
of glucocorticoids on bone would predominate and
oppose any effect of vitamin D in increasing bone
resorption.

Bendrofluazide decreases urinary calcium and this
may be accompanied by a slight rise in faecal calcium,
calcium balance remaining unchanged (Nassim and
Higgins, 1965).

The three drugs glucocorticoids, bendrofluazide
and vitamin D can, therefore, oppose the individual
actions of one another.

It has been shown that the negative calcium
balance and hypercalciuria which occurs when glucocorticoids are administered can either be corrected (Cases 1 and 2) or prevented (Case 3) with vitamin D and bendrofluazide given together. Prednisolone would be expected to minimize any rise in plasma calcium due to vitamin D therapy, and bendrofluazide to reduce urinary calcium and prevent hypercalciuria. Administration of an adequate dose of vitamin D is important; this is well demonstrated in Case 2 in whom 1 mg of calciferol in combination with 5 mg of bendrofluazide induced zero balance, whereas reduction of calciferol to 0·5 mg/day caused a rise in faecal calcium which resulted in a negative calcium balance.

Thus by antagonizing the various actions of one another, vitamin D, bendrofluazide and glucocorticoids in combination can improve calcium balance with little risk of hypercalcaemia. On the other hand hypercalcaemia developed as calcium balance became more positive in patients not given glucocorticoids (Cases 4 and 5) and, as with intravenous calcium therapy, renal damage may occur (Bodfors, Lindahl and Lindahl, 1974).

Further studies are now required to assess whether correction of the hypercalciuria and negative calcium balance induced by glucocorticoids reverses or prevents the development of steroid-induced osteoporosis.

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