PAPERS AND ORIGINALS

Osteoporosis and Long-term Corticosteroid Therapy

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Summary

Sequential measurements of total body calcium by in-vivo neutron activation analysis were made in five patients treated with corticosteroid drugs for severe inflammatory disease. No evidence of osteoporosis was seen to develop during the course of 20-33 months of study. In one case a substantial rise in total body calcium was found.

Introduction

The development of osteoporosis, and particularly vertebral collapse, is commonly regarded as a constant danger of long-term corticosteroid therapy. In some cases it may be the unfortunate price which has to be paid for control of such diseases as rheumatoid arthritis, nephritis, or asthma. The criteria which are used to define the presence of osteoporosis clearly affect the reported incidence of this complication of corticosteroid drugs. Studies which rely on the development of relatively late features of osteoporosis, such as loss of height or radiological evidence of vertebral collapse (McAllen, 1970), may tend to underestimate the true incidence of bone disease. Conversely the use of x-ray densitometry (Cameron *et al.*, 1968) detecting in practice $\pm 4\%$ changes in bone mineral content (Johnston *et al.*, 1968) may suggest a much higher incidence of this complication of corticosteroid drugs (Bjelle and Nilsson, 1970; Mueller *et al.*, 1970).

The disadvantage of these densitometric techniques is that they rely on measurements made on limb bones though the peripheral and axial skeletons may not necessarily be symmetrically involved in osteoporosis (Nordin, 1971). Measurement of total skeletal calcium might avoid difficulties in asymmetry of the osteoporotic process, and the present study discusses the application of in-vivo neutron activation analysis to this problem. The neutron activation technique (Anderson *et al.*, 1964;

Chamberlain *et al.*, 1968; Palmer *et al.*, 1968; Cohn *et al.*, 1970) depends on the induction of the radioactive isotope ^{45}Ca from stable ^{48}Ca by in-vivo neutron bombardment. The induced radioactivity can be measured by external counting and provides an index of total body calcium. The method used in the present study (Chamberlain *et al.*, 1970) makes it possible to measure sequential changes in total body calcium with an accuracy of $\pm 4\%$ (Hosking *et al.*, 1972 a). Since less than 1% of the calcium in the body lies outside bone such measurements represent, for practical purposes, changes in total skeletal calcium. Whole-body neutron activation analysis is more sensitive than conventional radiology and may provide useful, additional, and complementary information to that obtained by densitometric techniques.

The present study reports the results of sequential measurements of total body calcium using an in-vivo neutron activation analysis technique.

Patients and Methods

Five patients treated with long-term corticosteroid therapy were studied for periods of 20-33 months. During the study the underlying disease process was controlled by corticosteroid therapy in all of them. Admission to hospital was infrequent and all remained fully ambulant.

Corticosteroid dosage is shown in fig. 1. Plain radiographs of the skeleton in cases 1-4 were normal throughout the study. There was, however, qualitative evidence of mild rarefaction of the thoracic and lumbar spine in case 5 in February 1970, but radiographs in October 1971 were considered to be normal.

Case Reports

Case 1.—A 56-year-old woman had active chronic hepatitis diagnosed in December 1967. Jaundice was controlled by prednisone, though relapses in March and September 1969 required increases in dose. She remained symptomatically well, though tests of liver function were mildly abnormal, but has not required hospital admission since December 1967.

Case 2.—A 28-year-old woman had active chronic hepatitis diagnosed in February 1969 after admission to hospital with a haematemesis. Liver disease was controlled by prednisone but evidence of steroid toxicity developed. Attempted substitution by azathioprine led to a relapse and prednisone was recommenced with

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FIG. 1—Corticosteroid dosage of five patients studied. Arrows indicate dates of measurements of total body calcium.

control of hepatocellular damage once more being achieved. She remained clinically well.

Case 3.—A 34-year-old man presented with a respiratory illness due to polyarteritis nodosa in June 1969. There was an immediate clinical response to ACTH, which was subsequently maintained by prednisone. All parameters of disease returned to normal and the patient remained well.

Case 4.—A 24-year-old woman developed systemic lupus erythematosus in April 1966 but was controlled by betamethasone (fig. 1). The disease relapsed in December 1968 and she was admitted to hospital where prednisone was begun. Further admissions and increases in steroid dosage were required in March and August 1969. A relapse in January 1972 was treated successfully as an outpatient with a temporary increase in steroid dose. Since August 1969 she has generally been well and working full time.

Case 5.—A 41-year-old man developed jaundice in November 1964 which was found to be due to active chronic hepatitis. Remission obtained by large dose of prednisone but signs of steroid overdosage appeared. Less evidence of toxicity was apparent with the substitution of betamethasone. Mercaptopurine was added in May 1968 with improved control of hepatocellular damage.

The present study uses the ^{45}Ca activity induced by in-vivo neutron bombardment as an index of total body calcium. The theoretical and practical details of this technique have previously been described (Chamberlain *et al.*, 1970; Hosking *et al.*, 1972 a). Total body calcium is not expressed in absolute units but as a ratio of induced ^{45}Ca activity to the total neutron dose received.

Patients were studied at about six-monthly intervals and results given as the percentage change in total body calcium when compared to the initial measurement arbitrarily taken as 100%.

Provided that the distribution of osteoporosis does not change during the period of the study, its asymmetry does not adversely affect the precision of this technique.

Results

The results of sequential measurements of total body calcium are shown in the table.

Results of Sequential Measurements in Patients under Study

Case No.	Date	Weight (Kg)	Neutron Dose	^{45}Ca Activity	^{45}Ca Activity	Percentage Change
					Neutron Dose	
1	24.9.69	68.7	7,092	1,443	2034	—
	8.7.70	68.7	7,254	1,418	1954	-3.9
	3.2.71	68.1	6,766	1,372	2027	-0.4
	21.7.71	67.5	6,761	1,360	2011	-1.1
	22.12.71	63.2	4,350	910	2091	+2.8
2	14.4.69	60.3	6,836	1,509	2207	—
	10.12.69	66.3	6,055	1,365	2254	+2.1
	24.6.70	60.9	6,161	1,381	2241	+1.5
	6.1.71	63.5	6,426	1,422	2212	+2.2
	5.8.71	60.9	7,058	1,477	2093	-5.2
3	19.1.72	61.0	6,368	1,390	2182	-1.2
	24.9.69	91.1	7,064	2,195	3107	—
	15.4.70	88.7	6,499	2,040	3138	+1.0
	11.11.70	86.6	6,933	2,162	3118	+0.4
	23.6.71	86.5	6,801	2,075	3051	-1.8
4	19.1.72	89.4	6,084	1,812	2977	-4.2
	24.9.69	55.8	7,149	1,546	2149	—
	9.6.70	54.5	6,562	1,414	2154	+0.2
	6.1.71	55.5	6,593	1,427	2164	+0.7
	7.7.71	53.9	7,068	1,496	2116	-1.5
5	22.12.71	56.0	6,918	1,502	2171	+1.0
	17.3.70	82.2	6,472	1,443	2229	—
	28.10.70	69.6	6,663	1,510	2266	+1.6
	9.6.71	63.0	6,654	1,760	2645	+18.6
	24.11.71	61.2	6,713	1,688	2514	+12.6

Neutron Dose = Total dose received during activation (counts/316 sec). ^{45}Ca Activity = Counts/256 sec.

In cases 1-4 all but two measurements of total body calcium are within $\pm 4\%$ of the initial value. The fifth measurement in case 2 (-5.2%) does not appear to represent a consistent change while the fifth measurement in case 3 (-4.2%) is only just outside the 95% confidence limits of this technique. In general the sequential measurements in the first four cases suggest that there has not been a significant change in total body calcium during corticosteroid therapy.

A considerable increase in total body calcium was detected in case 5 during the latter part of the study, in that there was a rise of 11% between October 1970 and November 1971. It is most improbable that the observed increase was an artefact due to the change in body weight which occurred during the period of study. The likely cause of the increase is discussed below.

Discussion

The ability of the in-vivo neutron activation technique to detect sequential changes in total body calcium in metabolic bone disease has previously been described (Hosking *et al.*, 1972 a, 1972 b; Hosking and Chamberlain, 1973). In osteoporosis the mineralized bone mass per unit volume is reduced but the bone is in other respects normal (Nordin, 1971). In these circumstances a decrease in total body calcium may be taken as a reasonable index of developing osteoporosis. The lack of change in total body calcium in the first four patients treated with corticosteroids suggests, therefore, that if osteoporosis has developed during the course of the study then this represents a loss of less than 4% of the total skeletal calcium.

In some of the earlier reports of osteoporosis occurring during corticosteroid treatment (Demartini *et al.*, 1952; Curtiss *et al.*, 1954; Reifstein, 1958) additional factors such as immobilization and the effect of ageing make it difficult to assess the role of corticosteroids in the production of osteoporosis. Even though the patients with corticosteroid-treated asthma reported by McAllen (1970) were fully ambulant, most of the cases who developed osteoporosis were over the age of 60. In diseases where immobilization is not a prominent feature or where a generally younger age group is involved, osteoporosis appears to be a less common complication of corticosteroid therapy. In 18 cases of systemic lupus erythematosus (all but two aged less than 40 years) who were treated with long-term corticosteroid therapy only one, a woman of 58, developed osteoporosis (Soffer and Bader, 1952). Nor was there evidence of osteoporosis in a group with corticosteroid-treated allergic

disorders (Klein *et al.*, 1965) who were otherwise fit and well. In all these studies the dose of corticosteroid was comparable to that received by the present patients. It would seem probable, therefore, that corticosteroid therapy given in moderate dosage for up to three years to relatively young and ambulant patients is unlikely to be complicated by osteoporosis. Total body calcium in case 5 increased significantly over the period of study. There are three factors which may be involved. Firstly, a change in the thickness of subcutaneous tissues may alter the neutron flux incident on the skeleton. Experiments using polypropylene phantoms have shown that a change of more than 1 cm in moderator—that is, subcutaneous fat—thickness is required before there is a significant alteration in the activating neutron flux (Holloway, 1970). Though there was a considerable change in weight during the study there was no reduction of fat fold thickness (Fletcher, 1962) of this order of magnitude. In fact no change in total body calcium was detected during the first six months of study when weight loss was most pronounced. It is unlikely, therefore, that the measured changes in total body calcium were attributed to alteration in body habitus.

A second factor which may be relevant is the improved control of hepatocellular damage which was achieved in the last year of study (fig. 2). Osteoporosis may occur in chronic liver disease (Paterson and Losowsky, 1967) of comparable severity to the present case. Osteomalacia has not been excluded in this case by means of bone biopsy, but in the absence of biliary cirrhosis or obstruction it is probably uncommon. However, the improvement in liver function which occurred during the period of study hardly seems to be of sufficient magnitude to account for such a noticeable change in total body calcium. Such a rise implies reversal of a previous phase of osteoporosis, though this type of bone disease is generally thought to be irreversible (Rose, 1967).

Alternatively it may be that the increased well-being and improved liver function as a result of corticosteroid treatment led to increased ambulation and reversal of the osteoporosis of immobilization. In support of this view is the report by Donaldson *et al.* (1970) who used γ -ray transmission scanning of the os calcis during immobilization. The loss of bone mineral which occurred to a greater extent in the weight-bearing bones than in the remainder of the skeleton appeared to be reversible after ambulation. Similar evidence of an increase in bone mineral content in response to physical activity was also found by Smith (1971) using a γ -ray densitometry study of the midshaft of radius. It may be that in the treatment of severe diseases with corticosteroid drugs any tendency to produce osteoporosis may be more than compensated by the return of well-being and mobility produced by this form of therapy.

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FIG. 2—Case 5. Corticosteroid dosage, liver function, and changes in total body calcium.

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