

Oral Calcium-loading Test in Infancy, with Particular Reference to Idiopathic Hypercalcaemia

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Summary: An oral calcium-loading test suitable for infants is described and the usual response defined. In four acute cases of idiopathic hypercalcaemia a high and sustained rise in serum calcium occurred, suggestive of hyperabsorption and consistent with a vitamin-D-like effect. In four further infants with a milder illness suggestive of hypercalcaemia the fasting calcium levels were not grossly raised, but the test produced an exaggerated hypercalcaemic response. In this type of patient the test is more sensitive in the diagnosis of idiopathic hypercalcaemia than isolated measurements of serum calcium, especially if these are taken in the fasting state. Five patients on treatment and three whose treatment had been discontinued (but who subsequently relapsed or made a poor recovery) showed abnormal loading tests at a time when fasting calcium levels were normal. In two cases full recovery from the disease was associated with reversion of the test to normal. The test can therefore be used to indicate activity of the disease and consequently as a guide to therapy. In two cases a persistently abnormal loading test was associated with a poor long-term prognosis.

Introduction

In childhood, dynamic studies of calcium metabolism have mostly involved balance procedures which may present technical difficulties and have other limitations (Isaksson and Ohlsson, 1967; Isaksson and Sjögren, 1967; Isaksson *et al.*, 1967), intravenous calcium infusion tests have been used (Cassimos *et al.*, 1963; Vaandrager and Weyers, 1963; McCredie and McIntyre, 1968), and radioactive isotope studies have been made in a variety of disorders (McCredie and McIntyre, 1968), including vitamin-D-deficiency rickets (Harris *et al.*, 1965) and vitamin-D-resistant rickets (Joseph *et al.*, 1963). Oral calcium-loading tests have been described in adults in the investigation of hypoparathyroidism (Jones and Fourman, 1963), hypothyroidism (Lowe *et al.*, 1962), and idiopathic hypercalcaemia (Peacock *et al.*, 1968).

In this study a calcium-loading test designed to measure the effect of a standard dose of oral calcium on short-term changes in the serum calcium level was carried out in a number of miscellaneous disorders not usually associated with recognizable disturbance of calcium metabolism, and in idiopathic hypercalcaemia at various stages of the disease.

Patients, Procedures, and Methods

The miscellaneous group comprising 15 infants aged from 2 months to 2½ years included cases of anaemia, respiratory infection, and congenital malformation. All were on normal infant or toddler diet without vitamin D supplements.

In 12 patients idiopathic hypercalcaemia was diagnosed at ages ranging from 6 to 11 months on the basis of clinical signs

and symptoms along with varying degrees of hypercalcaemia, hypercalcaemia, raised blood cholesterol, and radiological change. Four of the cases were acute and of the so-called "mild" type (mean duration of symptoms before diagnosis 9 weeks; range 6 to 12 weeks). Four cases with apparently less serious symptoms (mean duration of symptoms before diagnosis 15 weeks; range 6 to 20 weeks) included two also classified as "mild" and two which, because of the subsequent course of their illness, would be classified as "severe." Two further patients with the mild type of hypercalcaemia were first studied after three and four months of therapy. Two older children, aged 6 and 7 years, were typical survivors of the severe type of hypercalcaemia.

For the test procedure older infants were fasted overnight. Babies had the preceding bottle-feed one hour early to ensure a four- to five-hour fast. The test feed was composed of calcium lactate 385 mg./kg. body weight (50 mg. of calcium per kg. body weight), dissolved by heating in 5% dextrose solution (30 ml./g. of calcium lactate). Younger infants took the feed from a standard feeding-bottle within about 15 minutes. Older infants drank it from a cup or received it by nasogastric tube over a 10-minute period. Vomiting occurred infrequently, and when it did the test was abandoned. Capillary blood specimens were taken by heel stab. The programme for the test was as follows:

Fasting specimen (1) at 0 time.

Test feed started at 0+15 minutes and continued till feed completed—usually 10-15 minutes.

Specimen 2 at 0+60 minutes—that is, 45 minutes after start of feed.

Specimen 3 at 0+120 minutes.

Specimen 4 at 0+180 minutes.

Specimen 5 at 0+240 minutes.

Total serum calcium was estimated by the method of Wilkinson (1957) involving E.D.T.A. titration with murexide as indicator.

Results

Miscellaneous Group

The group of 15 miscellaneous disorders all showed normal fasting calcium levels and a similar pattern of response. It thus appears justifiable to consider this group as a homogeneous control group. The mean values and range based on ± 2 S.D. are shown in Fig. 1. The mean fasting level was 9.7 mg./100 ml., and after the standard test feed there was an average rise to a peak value of 10.7 mg./100 ml. at two hours, with a subsequent fall to 10.0 mg./100 ml. at four hours.

Idiopathic Hypercalcaemia

Results in the four patients tested in the acute phase of the disease are shown in Fig. 2. Fasting calcium levels were high (mean 13.5 mg./100 ml.; range 12.8 to 14.9 mg./100 ml.), and after the test feed marked hypercalcaemia developed. One patient received half the standard dose of calcium and showed a lesser response. Tests in the four less seriously affected patients, who presented with features suggestive of idiopathic

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hypercalcaemia, are shown in Fig. 3. Previous to any form of treatment the fasting calcium levels were only moderately raised (mean 10.9 mg./100 ml.; range 10.5 to 11.3 mg./100 ml.). The response to the test feed showed peak values of serum calcium greater than 13 mg./100 ml. and calcium levels of 12 mg./100 ml. or more persisting to four hours in each case.

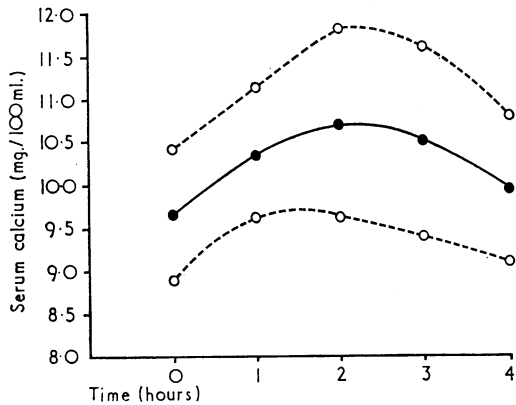


FIG. 1.—Calcium-loading test-response in 15 control infants. Mean \pm 2 S.D.

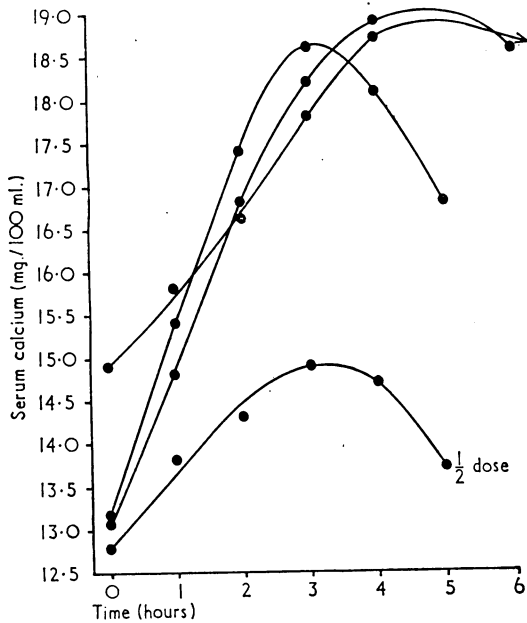


FIG. 2.—Calcium-loading tests in idiopathic hypercalcaemia with marked hypercalcaemia—four cases in acute phase.

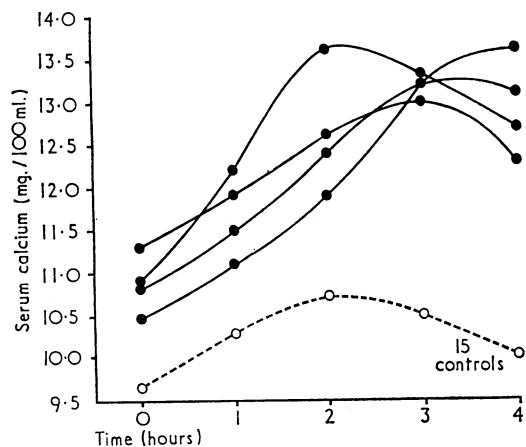


FIG. 3.—Calcium-loading tests in idiopathic hypercalcaemia—four cases with minimal hypercalcaemia.

The effect of therapy in the four acute cases (Fig. 2) is shown in Fig. 4. After four to six weeks on a low-calcium diet, with prednisolone in three cases, all were symptomatically much improved. Fasting calciums were normal, but each case showed an exaggerated response to the test feed, with values greater than 12 mg./100 ml. persisting to four hours.

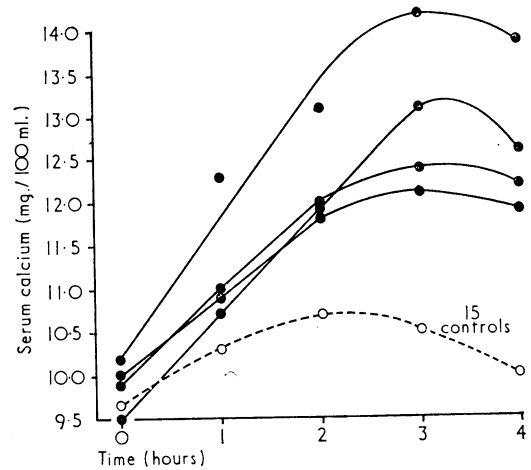


FIG. 4.—Calcium-loading tests in idiopathic hypercalcaemia—four acute cases on low-calcium diet, three also on steroids.

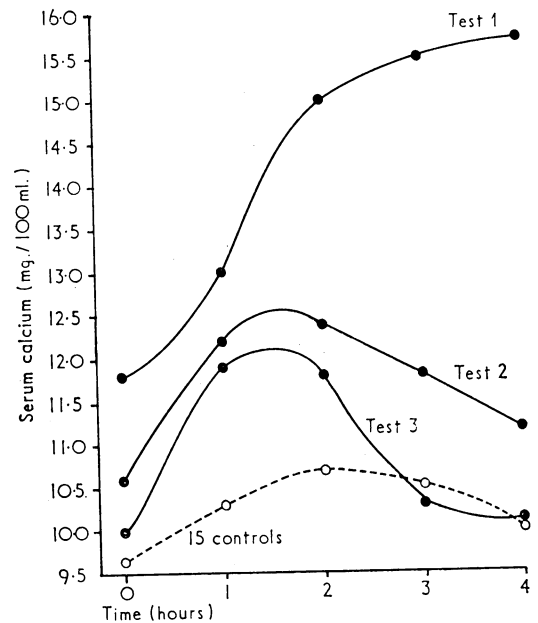


FIG. 5.—Calcium-loading tests in relapse of idiopathic hypercalcaemia—serial observations with recovery on low-calcium diet.

Serial observations during recovery were made on one of the less seriously affected patients with the so-called mild form of the disease (Fig. 5). Test 1 was performed during clinical and biochemical relapse. After three weeks on a low-calcium diet the fasting calcium and loading response had altered considerably (test 2). Three months later the curve (test 3) was approaching the mean of the control group.

Fig. 6 shows results in four infants after apparent clinical recovery from idiopathic hypercalcaemia. Treatment had been discontinued for periods of 10 days to two months. Fasting calcium levels were normal in two cases and at the upper limit of normal in the other two. Three cases showed values greater than 12.5 mg./100 ml. at four hours, and two of these subsequently relapsed and the other failed to thrive. The fourth case showed a response similar to that of the normal control group and remained well.

Fig. 7 shows the results in two infants who were studied some time after the original diagnosis of idiopathic hypercalcaemia and in whom the severe type of idiopathic hypercalcaemia in a chronic phase seemed to be present. At three months and seven months from presentation the fasting calciums were normal, but levels of 12 to 13 mg./100 ml. were obtained at three and four hours after the test feed. At three years from diagnosis peak values greater than 12 mg./100 ml. were obtained at two hours, but at each other stage in the test values were within the range of ± 2 S.D. from the mean of the control group.

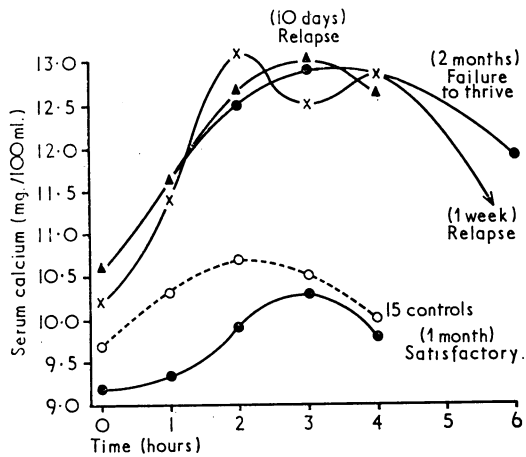


FIG. 6.—Calcium-loading test following apparent recovery in idiopathic hypercalcaemia—duration of treatment is indicated in parentheses.

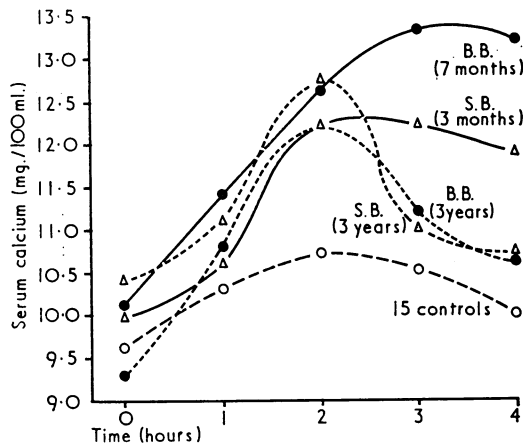


FIG. 7.—Calcium-loading test late in the course of two cases of idiopathic hypercalcaemia. Figures in parentheses = time from diagnosis.

Two further patients were typical survivors of the severe type. One case previously reported (Barr and Douglas, 1965) presented at the age of 6 years, having been in an institution without any special therapeutic regimen for a number of years. Her calcium-loading test showed a fasting value of 7.8 mg./100 ml. and at one to four hours values of 8.6, 9.2, 9.6, and 9.4 mg./100 ml. respectively. The second patient, aged 7 years, had been on a low vitamin D and moderately reduced calcium intake from the age of 7 months until three months before the calcium-loading test. This showed a fasting calcium of 9.6 mg./100 ml. and at one to four hours values of 10.5, 10.6, 10.4, and 9.8 mg./100 ml. respectively.

Discussion

The serum calcium response to a measured load of oral calcium depends on a number of factors, including dosage and type of calcium salt, concentration of calcium, and vehicle

used. These factors have been standardized in the present test. Changes observed in serum calcium are the resultant of a number of unmeasured variables. Absorption appeared to be the dominant influence over the first two hours when normally, as shown in the control group, the serum calcium rose by 1 mg./100 ml. on average (Fig. 1). Stabilization occurred over the next two hours as serum calcium equilibrated with the readily exchangeable calcium pool. These results apparently differ from the response in adults. Thus Peacock *et al.* (1968), using twice the dose of calcium (100 mg./kg.) in the form of the citrate salt, found a mean rise of 0.6 mg./100 ml. in three and a half hours, with a plateau for a further two to three hours. There is evidence that calcium absorption in infancy is more efficient than in the adult (Harrison, 1959), and it is probable that calcium transport differs, at least quantitatively, owing to the infant's exceptional requirements for bone growth.

In idiopathic hypercalcaemia the four acute cases (Fig. 2) had markedly raised fasting calcium levels. Unexpectedly high serum calcium levels occurred in the first three cases tested, and in the light of this we do not feel that the test should be applied to suspected cases of idiopathic hypercalcaemia if fasting calcium levels are greater than 12 mg./100 ml. The exaggerated response to oral calcium may denote hyperabsorption and is presumably part of the basic disturbance in idiopathic hypercalcaemia (Forfar *et al.*, 1956; Morgan *et al.*, 1956; Lindquist, 1962). It is consistent with the excess of vitamin-D-like activity found in the serum in some cases (Fellers and Schwartz, 1958; Kenny *et al.*, 1963).

Though in idiopathic hypercalcaemia the response to the calcium-loading test was found to be exaggerated, it was not possible to apply the test in other hypercalcaemic conditions such as hyperparathyroidism, where calcium tolerance might be quite different.

In the four cases which presented with only minimal hypercalcaemia (Fig. 3) the test showed impaired calcium tolerance. Two of the cases subsequently developed the full picture of idiopathic hypercalcaemia of the so-called mild type, and the test may therefore enable diagnosis to be made in the early stages of the disease before frank hypercalcaemia develops. The concept of idiopathic hypercalcaemia sine hypercalcaemia is not a new one (Forfar *et al.*, 1956, 1959). The other two cases developed a more chronic, low-grade disorder and eventual growth retardation, classified as the severe type.

Idiopathic hypercalcaemia is usually self-limiting, though the biochemical upset is of variable duration (Mitchell, 1960). The calcium-loading test reverted to normal with full recovery (Figs. 5 and 6), but when symptomatic and biochemical recovery was only apparent the test indicated that the disease was still active (Figs. 4, 5, and 6). In this respect the test is more sensitive than isolated fasting calcium levels, which may be normal during or for some time after a low-calcium diet (Figs. 4 and 6). If treatment is stopped prematurely, relapse may occur; if too prolonged, rickets may develop. Thus the test will indicate the desirability of stopping treatment as well as the need to continue it.

The two infants in Fig. 7 had the clinical picture of hypercalcaemia but only slightly raised serum calcium levels. Three months and seven months after presentation an abnormal loading test persisted, and three years from diagnosis the tests were still marginally abnormal. These boys are brothers who are dwarfed, intellectually impaired, and chronically constipated. They have abnormal facies with strabismus, malformed ears, and sparse hair, but do not resemble the negroid appearance associated with recovery from the so-called severe type of hypercalcaemia (Black and Bonham Carter, 1963). In these two cases abnormal calcium tolerance seemed to be an associated feature of their continuing disorder.

The two typical survivors of the severe type showed different responses. In one, despite the fact that the serum calcium level was below normal, the response would be regarded as

exaggerated by known infant standards. In the other a response similar to that of the control infants was obtained, suggesting that calcium tolerance was now normal. Further studies of calcium tolerance in late cases of idiopathic hypercalcaemia would be of interest.

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REFERENCES

- Barr, D. G. D., and Douglas, D. M. (1965). *Lancet*, 2, 1126.
 Black, J. A., and Bonham Carter, R. E. (1963). *Lancet*, 2, 745.
 Cassimos, C., Tsenghi, C., Michael, S., Liaromati, A., and Metaxotou, K. (1963). *Pediatrics*, 32, 272.
 Fellers, F. X., and Schwartz, R. (1958). *New Engl. J. Med.*, 259, 1050.
 Forfar, J. O., Balf, C. L., Maxwell, G. M., and Tompsett, S. L. (1956). *Lancet*, 1, 981.
 Forfar, J. O., Tompsett, S. L., and Forshall, W. (1959). *Arch. Dis. Childh.*, 34, 525.
 Harris, F., Hoffenberg, R., and Black, E. (1965). *Metabolism*, 14, 1101.
 Harrison, H. E. (1959). *Fed. Proc.*, 18, 1085.
 Isaksson, B., Lindholm, B., and Sjögren, B. (1967). *Metabolism*, 16, 303.
 Isaksson, B., and Ohlsson, L. (1967). *Metabolism*, 16, 295.
 Isaksson, B., and Sjögren, B. (1967). *Metabolism*, 16, 295.
 Jones, K. H., and Fourman, P. (1963). *Lancet*, 2, 119.
 Joseph, R., Mande, R., Job, J.-C., and Corbin, J.-L. (1963). *Arch. franç. Pédiat.*, 20, 699.
 Kenny, F. M., Aceto, T., Purisch, M., Harrison, H. E., Harrison, H. C., and Blizzard, R. M. (1963). *J. Pediat.*, 62, 531.
 Lindquist, B. (1962). *Acta paediat. (Uppsala)*, 51, Suppl. No. 135, p. 144.
 Lowe, C. E., Bird, E. D., and Thomas, W. C. (1962). *J. clin. Endocr.*, 22, 261.
 McCredie, D. A., and McIntyre, I. P. (1968). *Aust. paediat. J.*, 4, 47.
 Mitchell, R. G. (1960). *Arch. Dis. Childh.*, 35, 383.
 Morgan, H. G., Mitchell, R. G., Stowers, J. M., and Thomson, J. (1956). *Lancet*, 1, 925.
 Peacock, M., Knowles, F., and Nordin, B. E. C. (1968). *Brit. med. J.*, 2, 729.
 Vaandrager, G. J., and Weyers, H. A. (1963). *Ann. paediat. (Basel)*, 201, 287.
 Wilkinson, R. H. (1957). *J. clin. Path.*, 10, 126.

Sudden Failure of Swimming in Cold Water

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Summary: To investigate the effect of cold water on swimming four men who declared themselves good swimmers were immersed fully clothed on separate days in water at 23.7° and 4.7° C. The time that they were able to swim in the cold water was much shorter than in the warm. The two shortest swims ended after 1.5 and 7.6 minutes, before rectal temperature fell, when the men suddenly floundered after developing respiratory distress with breathing rates of 56-60/min. The other cold swims, by the two fattest men, ended less abruptly with signs of general and peripheral hypothermia.

It is concluded that swimming in cold water was stopped partly by respiratory reflexes in the thin men and hypothermia in the fat, and partly by the cold water's high viscosity. The longer swimming times of the fat men are attributed largely to their greater buoyancy enabling them to keep their heads above water during the early hyperventilation.

The findings explain some reports of sudden death in cold water. It is clearly highly dangerous to attempt to swim short distances to shore without a life-jacket in water near 0° C.

Introduction

Most deaths after shipwreck result from immersion hypothermia (Molnar, 1946; McCance *et al.*, 1956; Keatinge, 1965), but most deaths in inland waters are too rapid for this. For

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example, a good swimmer aged 20 recently disappeared within five minutes while he was trying to swim 50 yards (46 metres) to shore from an overturned dinghy in the calm water of a reservoir at 10-11° C. (Keatinge, 1969). Such accidents are often ascribed to cramp. However, sudden cooling of the skin causes breathlessness, which is accompanied by severe and often uncontrollable reflex hyperventilation (Keatinge and Nadel, 1965). This does not normally harm healthy people supported in cold water, but it seemed possible that it might prevent them from swimming.

The present experiments were designed to see whether good swimmers with clothes of a type worn by small-boat sailors could swim as far in water near 0° C. as in warmer water, and to see what eventually stopped them. Respiratory and temperature measurements were made by means that interfered as little as possible with respiration and with swimming.

Procedure and Methods

The subjects were four men aged 24 to 36 who declared themselves to be good swimmers. Subjects 1 and 4 were physiologists involved in the experiments, subject 3 was a student, and subject 2 an amateur dinghy sailor. Medical examination showed all of them to be free of cardiovascular or respiratory disease. Heights and weights were recorded and skinfold thicknesses were measured by callipers (John Bull British Indicators Ltd.) at four standard sites: biceps mid-way between acromion process and medial epicondyle of the elbow, subscapular over the lower corner of the scapula, abdominal 5 cm. below and lateral to the umbilicus, and subcostal at the lower border of the ribs below the mid-point of the clavicle.

Each man was immersed twice, first in an indoor swimming pool (water temperature 23.7° C., air 20.3° C.) and three weeks later (in March) in an outdoor pool (water temperature 4.7° C.,