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THE D VITAMINS AND DIHYDROTACHYSTEROL (DHT) IN METABOLIC DISEASES

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A large group of steroid-like compounds can cure rickets and are said to have Vitamin D or anti-rachitic activity. Those available for clinical use are:-

Calciferol (Ergocalciferol, Vitamin D_2.)

Cholecalciferol (Vitamin D_3.-the pure preparation is available only to hospitals).

Dihydrotachysterol (DHT)

The proprietary preparation "AT 10" now contains pure DHT, but was formerly prepared by the irradiation of ergosterol and then comprised a mixture of sterols with DHT as a main constituent.

All these compounds cure classical dietary rickets in microgram doses. Dosage was originally quoted in "international units" based on a standard assay in rachitic rats. One microgram of either calciferol or Vitamin D_3 is the equivalent of 40 international units DHT cannot be quoted in units. The use of units should now be given up and in the rest of the article reference is made only to micrograms and milligrams.

In the prevention or treatment of classical rickets, a daily dose of 10 micrograms of calciferol is sufficient and no difficulty is normally encountered though ten times this amount daily produces a more rapid cure and reduces the slight risk of temporary tetany on beginning treatment. Symptoms of over-dosage hardly ever occur with this larger dose.

These compounds are also used in the treatment of hypocalcaemic tetany and in metabolic bone disease, such as the osteomalacia or osteodystrophy that may occur in the malabsorption syndrome, in renal disease and in

a variety of rare hereditary conditions. When the primary disease cannot be treated by appropriate therapy, e.g., gluten-free diet for malabsorption or surgical relief of urinary obstruction causing renal failure, Vitamin D compounds must be used in doses 100 to 500 times greater than those effective in classical rickets-that is 1 to 5 milligrams (1,000 to 5,000 micrograms) daily.

With such large and unphysiological doses, overdosage readily occurs producing hypercalcaemia with severe lassitude, anorexia and eventual failure which may be irreversible. Some hypocalcaemic patients take a long time to respond to treatment, while others respond more quickly. The maximum action of a given dose may not be manifest for one to two months. Close biochemical and clinical control is needed in the early stages of treatment, and it is important to appreciate that the plasma calcium level today may reflect the daily dose given a month ago rather than that given in the last few days. Frequent change of dose should be avoided. A chart recording dosage, plasma calcium, inorganic phosphorus and alkaline phosphatase and clinical and radiological progress is useful in assessing the effect of treatment.

Dihydrotachysterol (DHT), although somewhat less effective than the other compounds in healing classical rickets, is probably a little more potent, weight for weight, when used for other purposes. It also acts a little more quickly and its effects wear off sooner if an overdose has been given. This confers a slight advantage which hardly offsets its much-greater cost. The sensitivity of an individual patient to a given dose of a given form of vitamin D may vary from time to time so that regular biochemical control is essential and a change from one preparation to another may be necessary.

Hypocalcaemic Tetany

The commonest cause of hypocalcaemic tetany is hypoparathyroidism. This most commonly follows subtotal thyroidectomy, but is occasionally idiopathic. Such hypocalcaemia always requires treatment to avoid long-term complications, even if the tetany is mild. Vitamin D should be given in one of its forms in a dose adjusted to maintain a normal plasma calcium. A loading dose of 5 mg (5,000 micrograms) is give daily for a

few days and this is then rapidly reduced to the expected maintenance dose of about 1 to 2 mg (1,000 to 2,000 micrograms) according to the plasma calcium rise achieved. Fractional milligram dosage is likely to be required and is difficult with capsules containing 1.25 mg. A scheme has usually to be worked out for each patient using dosages, such as two capsules every three days or one or two every other day. It is most important to have close biochemical control in the early stages, but once a maintenance dose has been worked out, a three-monthly check is usually sufficient. One should aim at maintaining normal (10.0 mg per 100 ml) or slightly subnormal (9.0–9.5 mg per 100 ml) levels. The rise in urinary calcium is so irregular that it cannot be used, as in the Sulkowitch test, as an index for regulating treatment. If the patient takes a daily glass of milk or otherwise has a reasonable and steady dietary calcium intake (600 mg or over), it is better not to supplement the action of Vitamin D by giving extra calcium. Most calcium tablets are unpalatable and likely to be omitted by the patient. Careful dosage regulation is more difficult if two preparations are given than when only one is used. Calcium alone in any dosage is quite inadequate treatment for any form of hypocalcaemic tetany. It produces only a small rise in plasma calcium with negligible symptomatic improvement and does not prevent the serious long term complications of hypocalcaemia, such as cataracts and calcification of the basal ganglia. Rarely hypocalcaemia is the result of one of the forms of steatorrhoea. If there is no specific treatment such as with a gluten-free diet, large doses of Vitamin D must be given as in hypoparathyroidism. Small doses suffice for gluten-sensitive patients given the appropriate diet.

Secondary Metabolic Bone Disease

In osteomalacia and in hyperparathyroidism secondary to otherwise incurable primary disease, Vitamin D is given in one of its forms and in comparable dosage to that given in hypocalcaemic tetany. The criterion for effective treatment however is not the plasma calcium level, which may be normal or subnormal, but a satisfactory healing response of the bone disease as shown by loss of bone pain, increased muscle strength, improvement in the X-ray appearances and the return to normal of the plasma alkaline phosphatase level. The essential principle of treatment

is that such healing should be induced with doses of Vitamin D which are not so large as to raise the plasma calcium to hypercalcaemic levels (about 10.5 mg per 100 ml). A daily loading dose of 5mg (5,000 micrograms) can be reduced in a few days to 1 to 2 mg (1,000 to 2,000 micrograms) per day and, once the bones are healed further reduction can be carried out to achieve a satisfactory maintenance dose (usually 0.25 to 1 mg daily). The maintenance dose varies from patient to patient and is usually lower in patients with steatorrhoea following partial gastrectomy and higher in those with other causes of steatorrhoea. Overdosage must be particularly avoided in patients with severe renal damage, since their renal reserve is already minimal.

Osteoporosis

This almost universal disease of old people, especially of women, is unfortunately not improved by Vitamin D.

Conclusions

Vitamin D used in large doses for the metabolic diseases referred to above is a most valuable drug when given in the right way to the right patients. It is always potentially dangerous since the therapeutic is never far from the toxic dose. In the British-born population of this country, Vitamin D is rarely required for the treatment of dietary rickets and if so very small doses are adequate. Prophylatic use is even less often indicated and hypervitaminosis with hypercalcaemia has been produced in the past by dried milks fortified with Vitamin D, since some young children appear to the quite exceptionally sensitive to the vitamin in only moderate dosage. Dietary rickets is more common in recently arrived immigrants, since they receive less exposure to sunlight than in their country of origin, may not be accustomed to eating foods containing adequate Vitamin D and may not avail themselves of the vitamin supplements distributed by Local Health Authorities. Dietary osteomalacia is also seen occasionally in adult immigrants and in British-born people in the geriatric age-group.

The current BNF does not make clear enough the fact that some standard doses of preparations of Vitamin D are about 100 times stronger than others.

The official preparations are:-

1. Capsules of Vitamins A & D (BPC)
   Each contains 11 micrograms of calciferol.
2. Calciferol Tablets B.P. (Synonym "Strong Calciferol Tablets".
   Each contains 1.25 milligrams (1,250 micrograms) calciferol.
3. Calciferol Solution B.P.
   Contains 0.075 mg (75 micrograms) per ml in vegetable oil.
4. Calcium with Vitamin D Tablets B.P.C.
   Each contains calciferol 12.5 micrograms, calcium sodium lactate 450 mg, calcium phosphate 150 mg.

The proprietary preparation "AT 10" contains 0.25 mg (250 micrograms per ml) of dihydrotachysterol in oily solution and is dispensed in 15 ml bottles.

It cannot be too strongly emphasized that Calciferol Tablets B.P. and "AT 10" should only be taken by patients under strict medical supervision. They are a therapeutic and not a prophylactic preparation and, if used for prophylaxis, may induce toxic effects. If Vitamin D is ever required prophylactically Calcium with Vitamin D Tablets B.P.C. are adequate. Even when the more potent preparations are indicated, great care is needed in specifying the dosage.

The theoretical basis of treatment with Vitamin D with a more detailed review of the clinical applications has been dealt with by the writer in two tape recordings available from the College of General Practitioners.

2. Calcium Supplements

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Calcium supplements are widely used, not always on a logical background of physiology. The indications must be related to the nutritional requirements of growth, maturity and reproduction, to the absorption of calcium, and to the needs of the skeleton in disease.