STUDIES IN RICKETS IN THE CAPE PENINSULA

V. THERAPY

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It is well known that vitamin D, taken orally, parenterally, or obtained from irradiation, prevents and cures ordinary rickets. We have, however, been impressed by a number of children who have developed rickets despite adequate exposure to sunlight, and we therefore wondered whether some children might not require considerably larger amounts of vitamin D than others. Indeed, Fanconi has suggested a continuous 'spectrum' in the degree of sensitivity to vitamin D.[1] We have observed the therapeutic effect of various doses of calciferol (this term is used synonymously with vitamin D) in an attempt to assess whether the individual requirement varies.

'AT 10' (dihydrotachysterol) has actions similar to calciferol, increasing calcium absorption from the gut and promoting a phosphorus diuresis.[2] This substance was first manufactured in Germany[3] and at that time was found to have no effect in curing rickets or raising the serum calcium in this condition.[4,5] This was ascribed to the fact that its main action appeared to be on phosphorus diuresis. More recent reports from Germany indicate that AT 10 may heal rickets.[6]

AT 10 resembles the parathyroid hormone in some ways and has been effective in the therapy of hypoparathyroidism, where AT 10 and vitamin D usually appear to be equally active on a weight basis (i.e. 1 mg. or 50,000 units of calciferol is equivalent to 1 mg. of AT 10).[7-9] McLean believed that 2 mg. of calciferol were equivalent to 1 mg. of AT 10 in activity.[10]

We have compared calciferol and AT 10 in their ability to heal clinical rickets. Forty-five children were treated with calciferol, 28 being given a single intramuscular injection of 1 ml. of 'ostelin forte'.** The remainder received oral therapy, either 'adexolin', 'vidaylin', or hake liver oil.*** Fourteen children were treated initially with AT 10.†

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** Ostelin forte [Glaxo-Allenbury (Pty.) Ltd.] — 1 ml. reputedly contains 600,000 units of vitamin D.

*** Adexolin [Glaxo-Allenbury (Pty.) Ltd.] — reputedly contains 10,000 units of vitamin D per oz.

*** Vidaylin [Abbott Laboratories (Pty.) Ltd.] — reputedly contains 800 units of vitamin D per oz.

*** Hake liver oil kindly supplied by Marine Oil Refinery, Simonstown (by courtesy of Dr. I. Robertson) — reputedly contains 4,000 units of vitamin D per oz.

† AT 10 ('hytakerol') kindly supplied by Winthrop Laboratories Ltd. (by courtesy of Dr. F. V. Stephen Lewis) — 15 ml. of AT 10 (corresponding to 1 bottle) is approximately equivalent to 800,000 units of vitamin D, assuming that 1 mg. of AT 10 is equivalent to 1 mg. of calciferol.

Vitamin-D Administration Before the Development of Active Rickets

An adequate history concerning previous vitamin-D therapy was obtained in 49 cases. In 22 of these the children had attended clinics and received oils — usually hake oil — as a prophylactic measure. The mother was able to assess the approximate amount taken by the child in 11 instances. Seven of these children had taken half a teaspoonful or more of hake liver oil daily for over 2 months before being seen with active rickets (i.e. an alleged total of at least 120,000 units of vitamin D).

RESULTS (TABLE I)

Intramuscular Vitamin D

Twenty-eight children received 1 ml. of ostelin forte and in 23 of them healing was evident after 3 months. In nearly all these children, especially the milder cases, radiological evidence of healing was present after 1 month. In moderate and severe rickets complete healing was usually not present after 3 months, and often took 5 - 6 months to appear. However, patients with equally severe lesions showed a marked variation in the time taken for complete healing to occur. Some children showed considerable, but not complete, healing after 10 months.

In 5 children no evidence of healing was observed after 1 ml. of ostelin forte. Two of these were only seen 6 weeks after therapy, and healing may have commenced later. There were, however, 3 patients in whom there was no healing after 3 months and who appeared resistant to this dose of vitamin D. Their histories were as follows:

1. G.L., aged 14 months, was first seen in March 1960 with gross rickets, and was given 1 ml. of ostelin forte. Six months later he still had active rickets and was given a further 1 ml. of ostelin forte. There was still no evidence of healing 1 month later and he was given a third injection of ostelin forte — a total of 1·8 million units of vitamin D. The rickets was still active 6 months after this, when he was 28 months old, and not yet walking.

2. J.W., aged 9 months, was seen in September 1959 and at that time had moderate rickets. He was given 1 ml. of ostelin forte and was seen at monthly intervals over the next 4 months. There was no evidence of healing. He was then given ultraviolet irradiation, but radiological appearances had deteriorated in March and May 1960. A further 1 ml. of ostelin forte was given in May 1960, but in August there was still no improvement. He then had a third injection of ostelin forte — a total of 1·8 million units of vitamin D. He was seen at monthly intervals over the next 3 months. By October 1960 early healing was evident and has progressed satisfactorily since then.

3. G.M., aged 10 months, had gross rickets when first seen in January 1959, and 1 ml. of ostelin forte was given at that time. Nine months later he still had gross rickets with generalized decalcification. A further 1 ml. of ostelin forte was given, and 3 months later there was radiological evidence of early healing.

TABLE I. PROGRESS AFTER 3 MONTHS' THERAPY

Treatment	*Severity of rickets*	*No. of patients*	*Healing*	*No healing*
Ostelin forte 1 ml. (600,000 units) intramuscularly	Severe	13	9	4*
	Moderate	10	9	1
	Mild	5	5	—
	Total	28	23	5
Adexolin (200,000-300,000 units) orally	Severe and moderate	8	8	—
Vidaylin (24,000-40,000 units) orally	Moderate	1	1	—
	Mild	2	1	1
Hake liver oil (orally):				
120,000 units	Moderate	3	0	3
240,000 units	Moderate	3	1 (slight)	2
720,000 units	Moderate	3**	3	0
AT 10 (15-45 ml.)	Severe	6	3	3
	Moderate	5	3	2
	Mild	3	1	2
	Total	14	7	7

*Two were only seen 6 weeks after therapy was given.
**Same patients as preceding three.

All these children had previously been exposed to 2 or more hours of sunlight daily. Their urine contained no albumin or sugar, nor were cystine crystals seen in the cornea. Their serum electrolytes were normal and none of them had renal calcification. There was no family history of rickets. Two of them showed evidence of healing, one after 1·2 million units of vitamin D, and the other after 1·8 million units, but the third child did not respond to 1·8 million units.

Oral Vitamin D — Adexolin and Vidaylin

Eight children with severe and moderate rickets received oral therapy with adexolin, so that a total of between 200,000 and 300,000 units of vitamin D was given over 4 - 6 weeks. In all cases healing was satisfactory within 3 months, and in some cases within 1 month. Three children, 2 with mild and one with moderate rickets, received smaller doses of vitamin D as vidaylin — a total of 24,000 - 40,000 units. No healing occurred in 1 child with mild rickets, but in the other 2 children healing was satisfactory.

Hake Liver Oil

Six children with rickets of moderate severity received oral vitamin D as hake liver oil. Three received one teaspoonful daily for 4 weeks (reputedly equivalent to 120,000 units of vitamin D) without any evidence of healing. The other 3 children received double this amount, but at the end of 1 month only 1 showed evidence of slight healing. The dose given to this second group of 3 children was doubled, 4 teaspoonfuls being given daily for 6 weeks (equivalent to 720,000 units of vitamin D). At the end of this time (now having received 960,000 units) complete healing had occurred in 1 child, while the other 2 showed considerable improvement.

AT 10 (Dihydrotachysterol)

Fourteen children with active rickets were given AT 10. Only 7 showed evidence of healing within 3 months. Two of these had received a total of 15 ml. of AT 10; 3 had been given 30 ml.; and 2, 45 ml. The other 7 children showed no evidence of healing after 3 months. Five of these had received 15 ml. of AT 10; 1, 30 ml. and 1, 45 ml. The outcome was not affected by the severity of the rickets. Five of the 7 children who showed no response to AT 10 were then given calciferol in equivalent dosage (600,000 units of vitamin D). In 4 children good healing occurred within 3 months. The other child was seen only 1 year later when healing was advanced, but not complete.

Rate of Healing

Twenty-five patients were seen monthly and showed good healing after 3 months. In 21 of these healing was present after 1 month, and in the remaining 4 after 2 months. The rickets was severe in 2 of these 4 and moderate in the other 2.

DISCUSSION

There appeared to be an individual variation in response to therapy, some children being more resistant to vitamin D than others. Children with equally severe rickets receiving the same therapy did not all respond in the same way. Most children responded satisfactorily to 1 dose of 600,000 units of vitamin D intramuscularly, though there were at least 3 children who were resistant to this. None of these 3 had evidence of renal or gastro-intestinal dysfunction. Two of these patients did respond to larger doses of vitamin D, but did not require the massive doses necessary to heal true vitamin-D-resistant rickets.

Relative resistance to vitamin D might also explain why some children developed rickets in spite of what would appear adequate prophylaxis. The potency of hake liver oil was proved by its ability to heal rickets when given in adequate dosage, but it did not appear satisfactory in doses which would be expected to have been sufficient on the basis of its alleged calciferol content.

An unusual sensitivity to vitamin D seemed to be present in those children whose rickets healed on very small doses of the vitamin — in fact it is surprising that

these children should have developed rickets at all. A sensitivity to vitamin D has been suggested as causing the syndrome of idiopathic hypercalcaemia, following the prophylactic fortification of foodstuffs with this vitamin in Britain.[11-13] No child in this series developed hypercalcaemia following vitamin-D therapy.

An individual variation in sensitivity to vitamin D may also explain differences in the rate of healing. Most children showed radiological evidence of healing after 1 month, probably earlier, but there were some children, especially with moderate or severe rickets, who took longer.

Calciferol therapy, irrespective of the mode of administration, appeared to be superior to AT 10 in healing rickets. Only half the children receiving AT 10 healed satisfactorily, while all of those who failed to respond to AT 10, and were then given equivalent doses of calciferol, healed satisfactorily. Apart from postulating individual variations, we see no obvious explanation for the fact that only some children healed on AT 10. Serum chemistry, social habits, and the dose of AT 10 administered, were similar in all patients.

The actions of AT 10 and calciferol differ. AT 10 is said to produce greater phosphorus diuresis (similar to parathyroid hormone) and to have less effect on gastrointestinal absorption of calcium. It is therefore not surprising that it is less efficacious in healing rickets.

SUMMARY

The effects of various therapeutic agents containing vitamin D and of AT 10 (dihydrotachysterol) were compared in 59 children with active rickets.

There appeared to be an individual variation in response to vitamin D. Five out of 28 children with ordinary vitamin-D-lack rickets were resistant to a single intramuscular dose of 600,000 units. The remainder healed satisfactorily on this dose, and some others healed on much smaller doses. The rate of healing also varied — some patients showed good healing after 1 month, others taking 3 or more months to show the same effect.

AT 10 was found to be distinctly less active than vitamin D in curing rickets. Hake liver oil, while certainly active in large doses, proved ineffective in doses which would have been expected to be therapeutically satisfactory.

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