Nephrotoxic Effect of Vitamin D Therapy in Vitamin D Refractory Rickets

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Hypophosphataemic vitamin D refractory rickets is a rare disease which may be inherited as a sex-linked dominant (Winters *et al.*, 1958), and is characterized by the development of the stigmata of rickets in the first year of life. There is often considerable delay before the correct diagnosis is made, and by then there may be some retardation of growth (Fraser and Salter, 1958). The rickets can be healed by very large doses of vitamin D (Albright, Butler, and Bloomberg, 1937), but the margin between the therapeutic dose and the toxic dose of vitamin D is small (Fraser and Salter, 1958). Vitamin D in toxic doses causes hypercalcaemia leading to nephrocalcinosis (Parfitt, 1964; David, Verner, and Engel, 1962).

We have recently studied 4 children with vitamin D refractory rickets to assess the likelihood of development of toxic effects from carefully monitored long-term treatment with vitamin D.

Material and Methods

Four children with hypophosphataemic vitamin D refractory rickets are the subject of this report. These children had developed rickets despite an adequate intake of vitamin D, and all had a low serum phosphate, normal serum calcium, and raised serum alkaline phosphatase at the time of diagnosis. Initial urinary studies showed excessive phosphate loss, normal amino acid excretion, and no reducing substances. They were treated with vitamin D, the dose being adjusted according to the values of the serum calcium and the 24-hour urinary calcium which were measured monthly; the results are summarized in Tables I and II. The serum phosphorus, alkaline phosphatase, latterly urea, and urinary phosphorus were also measured monthly, but the results are not reported here. Three of the children also received buffered isotonic sodium phosphate solution equivalent to 1.3 g. phosphorus daily. The rachitic deformities have improved and growth has been in the normal range. No child has had a urinary tract infection.

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Case Histories

Case 1. This girl was referred to hospital in 1962 at the age of 2 years with bowed legs. She had been fed on Cow and Gate milk from the age of 3 weeks, had started solids at 10 weeks of age, and had been given additional vitamins from the age of 1 month. On examination the wrists and ankles were swollen as were the costochondral junctions. There was 1.25 cm. between the knees with the malleoli touching. Her height was between the 3rd and 10th centiles for her age. An x-ray of the wrist showed healing rickets. The serum calcium was 10.0 mg./100 ml., phosphorus 2.5 mg./100 ml., urea 17 mg./100 ml., and alkaline phosphatase 27 KA units. She was treated with vitamin D₃, and for most of the time has received 1 mg. daily. Six months after treatment was started she developed symptoms of hypercalcaemia, with a raised serum calcium, and vitamin D₃ therapy was stopped for 2 months. Since then she has had two brief episodes of hypercalcaemia during which therapy has been stopped. Her rachitic deformities initially resolved, but recently she developed a mild genu valgum which was corrected with night splints. Her height is now on the 25th centile for her age (Fig. 1), and a recent x-ray of the wrist shows that the rickets has healed.

Case 2. When this girl was admitted to hospital in 1960 at the age of 2 years because she was not walking, she was found to have slight bowing of the legs, swelling of the wrists and ankles, and slight swelling of the costochondral junctions. She had received Cow and Gate milk and daily cod liver oil from the age of 1 month. Her height was on the 3rd centile for her age, and an x-ray of the wrist showed active rickets. The serum calcium was 8.9 mg./100 ml., phosphorus 2.4 mg./100 ml., urea 19 mg./100 ml., and alkaline phosphatase 66 KA units. She was treated with vitamin D₃ and isotonic buffered sodium phosphate solution. Despite full co-operation, control proved difficult and she subsequently developed hypercalcaemia on 5 occasions during which vitamin D₃ therapy was stopped. The phosphate solution was discontinued between September 1962 and April 1966. In 1965 craniectomy was necessary for relief of raised intracranial pressure due to complete craniosynostosis. Her height is now

TABLE I
Number of Monthly Measurements of Serum Calcium

Case No.	Duration of Treatment (yr.)	Serum Calcium (mg./100 ml.)				Total No. of Measurements
		<10	10-10.9	11-11.9	> 12	
1	5	36	18	1	3	58
2	7½	25	35	21	9	90
3	8	36	40	12	3	91
4	15½	65	80	21	7	173

TABLE II
Number of Monthly Measurements of 24-hour Urinary Calcium Excretion

Case No.	Duration of Treatment (yr.)	Urinary Calcium (mg./24 hr.)			Total No. of Measurements
		<100	100-199	> 200	
1	5	12	28	5	45
2	7½	65	12	6	83
4	15½	20	34	42	96

Note: Urine collections were unreliable in Case 3.

on the 25th centile for her age (Fig. 1) and the rickets is still slightly active radiographically, though she now has no skeletal deformities. She has received between 0.75 and 2 mg. of vitamin D₃ daily for most of the duration of treatment.

Case 3. This boy was referred to hospital in 1959 at the age of 9 years, with severe knock-knee, which had been first noticed at the age of 3 years. Mixed feeds had been started at the age of 6 months and he had been given cod liver oil intermittently from that age. He was found to have advanced knock-knee with 14.6 cm. of intermalleolar separation, and slight swelling of the wrists. His height was below the 3rd centile for his age and an x-ray of the wrist showed active rickets. The serum calcium was 8.7 mg./100 ml., phosphorus 2.1 mg./100 ml., urea 32 mg./100 ml., and alkaline phosphatase 39 KA units. His father also had bowed legs and the serum phosphorus was 2.9 mg./100 ml. He was treated with vitamin D₃ and isotonic buffered sodium phosphate solution. He has remained well, and his deformities have slowly resolved. His height is now on the 10th centile for his age (Fig. 2). A recent x-ray of the wrist showed that the rickets was still active. He has had 4 short periods of hypercalcaemia during which vitamin D₃ was discontinued. His dose of vitamin D₃ has varied between 2 and 6 mg. a day for most of the time since diagnosis.

Case 4. This girl was noticed to have bowed legs at the age of 20 months and was admitted to hospital in 1952 at the age of 4 years. Her general health had been good and she had had cod liver oil daily from the age of 4 months. She had marked bowing of the legs, with 7.6 cm. separation between the knees, and the

costochondral junctions were slightly enlarged. Her height was below the 3rd centile for her age. An x-ray of the knees showed late, slightly active rickets. The serum calcium was 11.4 mg./100 ml. phosphorus 2.2 mg./100 ml., urea 25 mg./100 ml., and alkaline phosphatase 55.8 KA units. She was treated initially with calciferol, but in 1956 treatment was changed to vitamin D₃ and from 1959 onwards she was given isotonic buffered sodium phosphate solution in addition. In 1954 she had a bilateral osteotomy of the tibiae. Her deformities have persisted, though improved by the osteotomy, and her height has continued on the 3rd centile (Fig. 1). X-rays of the wrist show that the rickets has not been active for the past 8 years. Her dose of vitamin D₃ has varied between 3 and 5 mg. daily since 1956, and she has had one prolonged, and three short, periods of hypercalcaemia.

Methods

The patients were admitted to hospital in 1968 for investigation of renal function. The urine was tested for protein by Albustix test tapes (Ames) and for reducing substances by Clinitest tablets (Ames). Creatinine clearance was measured twice during two consecutive 3-hour collections of urine with one blood sample taken between the collections. The serum and urine creatinine were measured on the Auto-Analyser using a modification of the standard Technicon method. The duplicate estimates of creatinine clearance all showed good agreement. The result is given as the mean of the two values corrected to a surface area of 1.73 m.² The extent to which the urine could be concentrated during a period of fluid deprivation was measured by weighing successive samples of urine in a specific

FIG. 1.—Growth chart (Tanner, Whitehouse, and Takaishi, 1966) showing height in Case 1 ●—●—●, Case 2 ○—○—○ and Case 4 ×—×—×.

FIG. 2.—Growth chart (Tanner et al., 1966) showing height in Case 3 ●—●—●.

gravity bottle and recording the time taken to achieve a specific gravity of 1022 or greater. The ability to excrete an acid load was assessed by performing the ammonium chloride test in the following manner. After collecting urine for about 2 hours a dose of ammonium chloride $\left(\frac{5 \text{ g.} \times \text{surface area (sq. m.)}}{1.73} \right)$ was given. Three further consecutive 2-hour urine specimens were collected, each accurately timed and immediately cooled to -20°C . to await analysis. Urinary ammonia was estimated by applying directly to urine the phenol-hypochlorite method, as described by Horn and Squire (1966). Titratable acidity was estimated using the method of Henderson and Palmer, as described by Peters and Van Slyke (1931), in which the urine is titrated to pH 7.4 using 0.1 N NaOH, with phenol red as indicator. The results were expressed as micro-equivalents of ammonia and titratable acid excreted per minute, both corrected to a surface area of 1.73 sq. m. The pH of the urine was measured with narrow range pH indicator papers. After intravenous pyelography, percutaneous renal biopsy was performed using local anaesthesia according to the method described by White (1963). The specimens were fixed in 10% formol saline, sectioned at 2–3 μ , and stained by Von Kossa's method and with haematoxylin and eosin, PAS, and Weigert's elastic van Gieson stain.

Results

The intravenous pyelogram was normal in the 4 children, and their urines did not contain protein

or reducing substances. The results of the remaining investigations are shown in Table III. Creatinine clearance was normal in 3 cases, but reduced to half in Case 2. All 4 cases were able to concentrate urine satisfactorily. The ammonium chloride load test was abnormal in all. Case 2 was unable to excrete urine with a pH below 5.8, ammonia excretion was impaired in all, and the urinary titratable acidity was just below normal in Cases 1 and 4.

Renal biopsy was performed in Cases 1, 2, and 3. The specimens from Case 1 consisted of cortex and medulla and contained 17 glomeruli: these showed slightly increased cellularity and slight increase of centrilobular fibrillary material. Calcification was present in several areas within the medulla related to the tubules (Fig. 3). The specimens from Case 2 consisted of cortex only and contained 37 glomeruli. Almost half the glomeruli were sclerosed, and several others were partially sclerosed. In several glomeruli there was a moderate amount of endothelial cell proliferation, with loss of capillary spaces, and there were many deposits of calcific material in the interstitial tissues, but none in the tubules or glomeruli (Fig. 4). The specimens from Case 3 consisted of cortex and medulla, and contained 18 glomeruli, of which 2 were sclerosed and the remainder normal. Two small deposits of calcium were present related to

TABLE III

Results of Investigation of Renal Function in 4 Patients with Vitamin D Refractory Rickets

Case No.	Creatinine Clearance (ml./min. per 1.73 m. ²)	Urine Concentration Test SG of Urine	Ammonium Chloride Load Test		
			pH of Urine	Titrateable Acidity (μEq/min.)	Ammonia (μEq/min.)
1	96	1026 in 17½ hr.	5.0	23.5	14.5
2	52	1034 in 18 hr.	5.8	35.9	9.8
3	123	1027 in 16½ hr.	5.2	33	14.4
4	180	1025 in 16½ hr.	5.2	21	28.6
Normal	85-146*	1022† in 24 hr.	5.3 ‡ or less	24-51‡	33-75‡

* Winberg (1959). † Fishberg (1954). ‡ Wrong and Davis (1959); Matsuda *et al.* (1968).

the tubules, one in the cortex and one in the medulla (Fig. 5).

Discussion

These 4 children were considered to be suffering from vitamin D refractory rickets for which no cause could be found. None had evidence of malabsorption or of renal failure, and in no case was there an abnormal excretion of amino acids or reducing substances in the urine. They were treated with large doses of vitamin D, and in addition buffered isotonic sodium phosphate solution was given to 3 of them, as recommended by West *et al.* (1964). The dose of vitamin D₃ was adjusted so that as far as possible the monthly serum calcium level was maintained below 11 mg./100 ml. in the early years and below 10 mg./100 ml. during the past 3 years. The control with vitamin D therapy has been best in Case 1, with only 7% of the monthly serum calcium measurements over 11 mg./100 ml. Control in Cases 3 and 4 has been moderately good, with approximately 15% of the monthly serum calcium measurement over 11 mg./100 ml. Despite full co-operation and careful monitoring, control has been poor in Case 2 who has suffered from 5 periods of hypercalcaemia, the serum calcium having been above 11 mg./100 ml. for one-third of her period of therapy.

There was no correlation between the 24-hour urinary calcium excretion and the subsequent development of renal damage; Case 2 has had a urinary calcium excretion over 100 mg. in 24 hours for only 20% of the duration of her therapy, and has been found to have severe renal damage, whereas Case 1 has had a urinary calcium excretion over 100 mg. in 24 hours for approximately 70% of the duration of therapy and has only a little

calcium deposited in the kidney. This lack of correlation may be due to Case 2 having a low glomerular filtration rate impairing calcium excretion, or to the wide range of normal 24-hour urinary calcium excretion (Knapp, 1947), which varies with calcium intake and body weight.

Growth in each case has been within the normal range after an initial period of acceleration in 3 patients. In Case 4 it has only been on the 3rd centile.

In 3 of the patients, investigations show that renal function is normal apart from slight impairment of urinary acidification, compared with normal values obtained by Wrong and Davis (1959) in adults, and by Matsuda, Takeda, and Shida (1968) in children. However, both these groups used a somewhat larger dose of ammonium chloride (0.1 g./kg. body weight) than that given to our patients. This difference may also in part explain the reduced excretion of ammonia in our patients. Renal biopsy in 2 of these patients shows only a few deposits of calcium. Therefore if hypercalcaemia can be avoided in the future the outlook for these patients is good. One patient has severe renal damage. Creatinine clearance is reduced by half, and she is unable to acidify the urine satisfactorily after an ammonium chloride load. In the kidney biopsy specimen, half of the glomeruli are sclerosed and numerous deposits of calcium are present.

Glomerular damage in nephrocalcinosis has been reported previously by Mortensen and Baggenstoss (1954) who found that though the medulla was predominantly involved, glomeruli were affected in a quarter of the cases, showing both hyalinization and cellular proliferation. Glomerular involvement has also been reported in hypercalcaemia due to

FIG. 3.—Renal biopsy from Case 1. (a) Several small deposits of calcium in the medulla. (Von Kossa. $\times 66$.) (b) Three glomeruli with slightly increased cellularity. (PAS. $\times 72$.)

thyrotoxicosis (Epstein, Freedman, and Levitin, 1958) and in idiopathic hypercalcaemia of infancy (Lowe *et al.*, 1954; Dawson, Craig, and Perera, 1954). We therefore conclude that the glomerular damage in this patient is a consequence of the repeated episodes of hypercalcaemia. The degree of glomerular involvement appears to be out of proportion to the amount of calcium in the specimen. However, it has been shown that calcium is removed from deposits in the kidney when the serum

calcium returns to normal (Kent *et al.*, 1958). This may well have occurred in this patient in the years since her last episode of hypercalcaemia.

Only one study of renal function and histology in children with vitamin D refractory rickets treated with large doses of vitamin D has been reported (Paunier *et al.*, 1968). 14 patients were studied, 13 of whom were found to have normal renal function. In 10 patients renal biopsy was performed and histology was normal in 8. One

FIG. 4.—Renal biopsy from Case 2. (a) Several small deposits of calcium in the cortex. (Von Kossa. $\times 66$.) (b) Four glomeruli, 3 of which are sclerosed and one partially sclerosed. (PAS. $\times 66$.)

patient with normal renal function had a moderate amount of calcium deposited in the medulla. The other patient whose renal function was impaired had sclerosed glomeruli and calcium deposits in the medulla. This patient had previously had a prolonged episode of hypercalcaemia and in addition suffered from chronic pyelonephritis. All these patients had had their vitamin D therapy carefully monitored by frequent estimations of the serum

calcium which was maintained below 10.5 mg./100 ml. as far as possible. Renal histology was also studied by Nigrin *et al.* (1962) in 8 patients with vitamin D refractory rickets treated with vitamin D, and 7 were found to have calcium deposits in the kidneys. Unfortunately renal function was not studied. The serum calcium level in these patients had not risen above 12.5 mg./100 ml. Robinson and Nelson (1945) found decreasing glomerular

FIG. 5.—Renal biopsy from Case 3. (a) Two deposits of calcium. (Von Kossa. $\times 66$.) (b) Two normal glomeruli. (Elastic van Gieson. $\times 66$.)

filtration rates in 2 patients with vitamin D refractory rickets treated with large doses of vitamin D.

The control of therapy in vitamin D refractory rickets is difficult, as the margin between the therapeutic and the toxic dose is small. Whereas the disease itself does not shorten life, nephrocalcinosis due to vitamin D intoxication may lead to chronic renal failure. It is therefore most important to avoid overdosage with vitamin D. Dent (1952)

recommended that the serum calcium should be maintained below 11 mg./100 ml., and thought that 'biochemical cure' should be the aim of treatment. In vitamin D intoxication, the urinary calcium excretion rises above normal before the level of serum calcium rises. Hence Stearns (1964) based the control of therapy on the 24-hour urinary calcium excretion related to the calcium intake for a given body weight, and aimed to keep

the urinary calcium excretion between plus and minus 3 standard deviations from the mean urinary calcium excretion (Knapp, 1947). Stamp *et al.* (1964), in 52 patients, tried to maintain the serum calcium below 12 mg./100 ml., and found it was impossible to prevent the recurrence of deformities or restore a normal growth pattern. Pierce, Wallace, and Herndon (1964) believed that the serum calcium level was the most important criterion of impending toxicity, and regarded a level of 11 mg./100 ml. or over as an indication for withdrawal of vitamin D therapy. A rigorous programme of splinting was recommended to check the progression of deformities before puberty. Fraser and Salter (1958) and Paunier *et al.* (1968) recommended that the level of serum calcium should be kept below 10.5 mg./100 ml. but found that growth was not always in the normal range, nor was complete 'biochemical cure' obtained.

Therapy in our children has not been as successful as in those described by Paunier *et al.* (1968), and even mild hypercalcaemia for only a few months in Case 1 has caused early nephrocalcinosis. We have therefore reviewed the control of therapy in our patients to see how nephrocalcinosis can be avoided. We think that therapy should be controlled by frequent measurements of the serum calcium level which should be kept below 10 mg./100 ml. as far as possible. Though a serum calcium level between 10 and 11 mg./100 ml. may not be toxic, by aiming for a lower level the serum calcium level is unlikely to rise above 11 mg./100 ml. should overdosage with vitamin D occur. If hypercalcaemia does occur, simple cessation of vitamin D therapy alone may be inadequate, and cortisone should be administered as this has been shown to cause a rapid reduction of the serum calcium in vitamin D intoxication (Winberg and Zetterström, 1956). In view of the lack of correlation between the urinary calcium excretion and the development of nephrocalcinosis, we do not think that control of therapy should be based on the urinary calcium excretion. We think that neither complete radiological healing nor 'biochemical cure' should be the aim of treatment, and prefer to keep the serum alkaline phosphatase between 20 and 40 KA units. Despite these criteria, it appears that growth may be in the normal range with early diagnosis and treatment. Nephrocalcinosis is insidious in onset, and repeated renal biopsy is not practical as a means of detection. However, measurement of glomerular filtration rate every 6 months appears to be a practicable investigation, a falling glomerular filtration rate being an indication for a careful review of renal function and therapy.

Summary

The danger of toxic effects of vitamin D therapy in children with vitamin D refractory rickets has been investigated by assessing renal function in 4 patients and renal histology in 3 of these patients, who have been treated for many years with large doses of vitamin D and whose growth has been within the normal range. All the patients showed impaired ammonia excretion during an acid load test. Other renal function tests were normal in 3 patients, 2 of whom had a few calcium deposits in the kidneys. One patient showed definite impairment of renal function, and renal biopsy revealed that half the glomeruli were sclerosed, and that there were numerous deposits of calcium in the kidney. Control of therapy in this patient had been difficult, and 30% of monthly serum calcium measurements were over 11 mg./100 ml. There was no correlation between urinary calcium excretion and renal damage. We conclude that 'biochemical cure' and complete radiological healing should not be the aim of treatment in vitamin D refractory rickets, and that therapy should be controlled by frequent estimations of the serum calcium which should be kept below 10 mg./100 ml.

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