Experience with refractory vitamin D-resistant rickets and non-17α alkyl testosterone derivative anabolic agent

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Background: Renal tubular disorders may be associated vitamin D-resistant rickets, dwarfism and deformities. Treatment is nonspecific and directed towards correcting acidosis, hypokalemia, hypophosphatemia and vitamin D resistance. The response to therapy depends on the severity of the disorder, and sometimes bone changes persist with the development of skeletal deformities. **Patients & methods:** From June 2000 to 2001, four patients with renal tubular disorder associated with vitamin D-resistant rickets and deformities despite previous therapies, were observed. Of these patients, three have hereditary (autosomal recessive) proximal renal tubular acidosis affecting siblings with perfectly normal parents and grandparents, including two sisters, and one patient has X-linked dominant hypophosphatemic rickets. All have at least one sibling who died affected by the same disorder. Two boys, each with proximal renal tubular acidosis and X-linked dominant hypophosphatemic rickets were enrolled in a clinical study investigating the possibility of adding nandrolone to their conventional therapies to promote healing of rickets, provided both were males and having markedly delayed bone age together with close monitoring of bone age and careful observation for any sign of virilization. The boy with X-linked dominant hypophosphatemic rickets aged 18 months at enrollment, continued to have severe active rickets with the development of kyphosis despite 5 months of combined therapy with 1-alfacalcidol and phosphate supplementation. He received seven doses of nandrolone decanoate (12.5 mg) every 4 to 5 weeks. The boy with proximal renal tubular acidosis was aged 7 years at the time of addition of nandrolone to the conventional therapies of alfacalcidol, alkali and potassium supplementation. He also demonstrated severe active rickets and worsening of his bowing deformities. He received ten injections of nandrolone (25 mg) every 2 weeks. Nutritional support was provided for both and their skeletal age was monitored biweekly. **Results:** The novel addition of nandrolone resulted in a perfect radiological healing of rickets and growth acceleration without the occurrence of unwanted effects or advancement of bone age. The two sisters did not show any clinical or radiological improvement in their rickets and one of them died within 6 months of referral. **Conclusion:** The judicious use of nandrolone in carefully selected patients with refractory vitamin D-resistant rickets and significant delay of bone age was associated with a beneficial effect on healing of rickets and growth without any obvious adverse effect. This beneficial effect has to be confirmed by additional trials in the future.

Keywords: nandrolone, refractory rickets, tubular defect, vitamin D

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Various functional renal tubular disorders (RTDs), such as renal tubular acidosis (RTA) and familial hypophosphatemia, are associated with renal bone disease and growth retardation. In these disorders, rickets is caused by hypophosphatemia and or acidosis. They have in common the ability to produce dwarfism and deformities and the characteristic of responding to appropriate, but differing therapy. Treatment of these disorders is commonly non-specific and directed towards correcting disturbances such as acidosis, hypophosphatemia, hypokalemia and vitamin D resistance. Response to therapies is dependent on the severity of the renal tubular defects. In some cases it is impossible to compensate the loss and treatment remains unsatisfactory, bone changes persist and the patients may be left with residual skeletal deformities [1–5].

Anabolic steroids prevent calcium and nitrogen loss in urine, increase protein anabolism and promote bone growth. Hence, this may be a worthwhile treatment option in some cases of dwarfism, provided bone age is well below chronological age. The main risk of overdose is in premature epiphyseal closure; however, this may be avoided by careful intermittent use and monitoring of skeletal maturation. Virilization is also a problem; however, methandienon and nandrolone are less virilizing than other anabolic steroids and have been used in women [6]. In

contrast to 17-α testosterone derivatives, nandrolone esters do not cause sodium sulfobromophthalein retention, therefore hepatic complications are infrequent with their use in ordinary doses for short periods [6,7]. The average recommended doses of nandrolone in infants is 12.5 mg intramuscularly and for children, 25 mg every 2 to 4 weeks [8].

Anabolic steroids lead to an improvement in growth in children with constitutional delay of growth and puberty without advancement in bone age when used for short periods, and also improved growth of peripubertal children with chronic renal failure. Experience with these agents in RTDs and vitamin-resistant rickets does not currently exist.

Patients & methods

From June 2000 to 2001, four patients with RTDs associated with vitamin D-resistant rickets and deformities despite previous therapies were observed. Of these patients, three have hereditary (autosomal recessive) proximal RTA including two sisters, and one patient has X-linked dominant hypophosphatemic rickets (XLHRs). All patients have at least one sibling who died afflicted with the same disorder. Two boys, each with proximal RTA and XLHR, were enrolled in a clinical study investigating the possibility of adding nandrolone to their conventional therapies to promote healing of rickets, stimulate growth and to provide early rehabilitation. Criteria for selection were:

- Male gender
- Severe rickets despite prior therapies
- Growth arrest and markedly delayed bone age
- History of seriously afflicted sibling (died)

Patient I

A boy with XLHR was referred for the first time at the age of 13 months with severe rickets (frontal bossing, bowing of long bones, kyphosis and marked growth retardation). He was diagnosed as having rickets at the age of 9 months, received vitamin D 600.000 i.u. in the form of a sterogyl drinkable ampoule. His weight at that time was 7 kg, and his height 66 cm, both at the third centile for age and gender. On referral 4 months later, his weight and height were the same (dropped below the third centile). In addition to rickets, he also has anorexia and skeletal aches and he was unable to bear weight. Radiographs showed diffuse rarefaction and widening, cupping and frying of the distal ends of the radius and tibia. Bone age was retarded – the hamate and capitate were absent (both usually present by 6 months). He has no history of polyuria, rapid breathing, photophobia or seizures. He has an older brother who died of the same illness after developing pneumonia and multiple fractures, including those of the ribs. His brothers received only large doses of vitamin D3 without any effect on rickets. There were also three other healthy siblings – two girls aged 17 and 19 years, respectively, and a 6 year old boy. The growth parameters of the healthy brother were above the 25th centile. The diagnosis of XLHR was based on persistent hypophosphatemia (serum phosphorus 2 mg), hyperphosphaturia urinary phosphate 2.8 g/24 h (upper limit of normal 200 mg/24 h). Normal serum calcium was 9 mg/dl without any evidence of Fanconi syndrome or RTA (serum potassium 4 mmol/L, serum chloride 110 mmol/L, serum bicarbonate 19.2 mmol/L, urine chromatography for aminoacids and sugars were negative).

The boy was initially treated traditionally with oral phosphate, a α-hydroxyvitamin D and nutritional support [11–13]. The starting dose of phosphate was 1 g daily and increased to 3 g daily by the end of the sixth week. No change in bowel motion was noted. The dose of 1-alfacalcidol ranged from between 0.1 to 0.4 µg/kg with frequent dose adjustment to keep serum calcium between 9 and 11 mg. Monitoring of serum calcium and phosphorus occurred every 2 weeks. After 3 months of treatment, it was possible to maintain serum phosphorus between 4 and 5 mg/dl, and after 5 months there were no more anorexia or skeletal pains and obvious lessening of kyphosis occurred. However, there was no effect on radiological healing of rickets and growth remained arrested. Nandrolone decanoate (ND) in a dose of 12.5 mg (deep intramuscular injections) [8] was administered every 4 to 5 weeks as adjunctive therapy aimed at promoting the healing of rickets and stimulating growth. A total of seven doses were administered.

Patient II

A boy with proximal RTA was first referred at the age of 7 years with severe bowing limb deformities. He was bed ridden and has never been able to stand or walk as skeletal pains and deformities had markedly limited his movement. Two affected siblings (brother and sister) died before reaching the age of 10 years. The boy was treated traditionally with 1-alfacalcidol, alkali and potassium supplementation up to the age of

2 years [1–3]. In the years since, he has been frequently hospitalized due to episodes of acidosis and hypokalemia – attributed mainly to the interruption of therapy. Even though long-term compliance was variable, he received traditional treatments regularly for at least 4 months without any beneficial effect on rickets. In recent years, repeated x-rays have failed to show any appreciable improvement in the radiological appearance of rickets. On referral, he was not clinically acidotic but showed signs of severe deforming rickets (frontal bossing, rachitic rosary, markedly swollen wrists and knees, and severe genu valgum). The spine was perfectly normal. The patient was resistant to touching or movement because of generalized skeletal pains and tenderness. His growth was assessed and recorded – height of 80 cm and weight 12 kg – both below the third centiles. Results of a radiograph of the wrist showed severe active rickets and a markedly retarded bone age – only the hamate and capitate were present at the carpus.

Laboratory tests

Serum calcium 8.8 mg/dl, serum phosphorus 3.3 mg/dl, serum bicarbonate 21 mmol/l and ND in a dose of 25 mg (deep intramuscular injection every 2 weeks) was added to his traditional treatment of which he received ten in total. The dose of 1-alfacalcidol ranged from between 0.2 and 0.4 μg/kg with frequent dose adjustment according to the serum calcium level which was monitored biweekly. Additional nutritional support was also provided. Close observation for any sign of virilization and biweekly monitoring of bone age at the wrist was ensured.

Patients III & IV

The two patients not enrolled were sisters with proximal RTA (hereditary). Upon referral, their ages were 9 and 11 years, respectively. Their growth was arrested – both had a height of approximately 80 cm and weight of 11.5 kg. They also had two affected siblings who died before reaching the age of 10 years. They were clinically not acidotic, although their long-term compliance with therapies was rather poor. Both had severe deforming rickets (rachitic rosary, swollen wrists and knees, bowing of forearms and femurs, and genu valgum). They also presented with skeletal pains and resisted touching during examination. They did not demonstrate spinal deformity. In addition to diffuse rarefaction, radiographs showed severe active rickets and retarded bone age.

Results

Patient I

In patient I, who presented with XLHR, perfect radiological healing of rickets occurred 5 months after the initiation of ND along with an associated onset of standing alone. At 9 months after the initiation of ND, bone age did not advance beyond the chronological age as indicated by the appearance of the hamate, capitate, epiphysis of radius, metacarpals and phalanges, while the triquetrum which usually appears during the third year was still absent [14]. A total of 18 months after the initiation of ND, height was recorded at 86 cm and weight at 11.5 kg, both at the tenth centiles, and the boy was walking steadily unaided. 22 months after the initiation of ND, height was recorded at 89 cm and weight at 12 kg. No sign of virilization or advancement of bone age beyond the chronological age was noted. Minor bowing of the forearm persisted; however, bowing of the legs was completely corrected.

Patient II

Clinical improvement was first noted during the fourth week after the initiation of ND heralded by the disappearance of skeletal pains and tenderness. By the end of the third month of therapy, perfect radiological healing of rickets was demonstrated in association with attempting walking. By the end of the fourth week the patient displayed a marked improvement in genu valgum and was walking confidently with little waddling, mainly due to the remaining bowing of the femurs with mild genu valgum. By the end of the fifth month of therapy, standing height was recorded at 90 cm and weight at 15 kg. The patient has never displayed signs of acidosis throughout the whole period of therapy, and apart from occasional sustained penile erections, no adverse effect was noted. Radiographs of the left wrist showed the appearance of the epiphysis of radius and the triquetrum (bone age equivalent to 3 years of age).

Patients II & III

These patients did not experience any clinical or radiological improvement. At 6 months after referral, the parents reported the death of the older sister at the district hospital where they reside. Cause of death was reported as pneumonia.

Discussion

Traditional RTD therapies remain unsatisfactory in some patients and various nontraditional therapies such as indomethacin and

growth hormone have been used in attempts to improve outcomes. However, there have been reports of patients developing deformities which have required surgical correction [1,2,4,5,11]. Even though non-α alkyl testosterone derivatives are not associated with hepatic damage in normal doses, they should be used with great caution in children due to their virilizing effects and the risk of premature epiphyseal closure. Anabolic steroids have been used in cases of dwarfism when the bone age is well below the chronological. Thus, bone age advancement can be avoided by intermittent use and close monitoring of skeletal maturation [6,7]. Experience with these agents in vitamin D-resistant rickets does not exist. Management of refractory disorders requires careful balancing of the possible unwanted side effects associated with persistant use in serious disorders, as the benefits in such cases may outweigh the possible risks, especially when these risks can be avoided through appropriately skilled use.

In addition to the beneficial effect on bone disease, the enrolled patient's experienced improved growth as both had experienced growth arrest for a long period of time which resulted in a drop in their growth parameters to a level far below the third centile. In both patients, growth parameters had reached or exceeded the third centile after treatment.

Conclusion

The judicious use of ND in carefully selected patients with refractory vitamin D-resistant rickets and significant delay of bone age was associated with a beneficial effect of healing rickets and growth without any obvious adverse side effects. The beneficial effect of ND in this study has to be confirmed by further trials as the small number of patients precludes the formulation of a definitive conclusion. However, trials of medications in large cohorts of children are never recommended in the first instance.

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