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Pharmacokinetics of sex steroids in patients with β thalassaemia major

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Abstract

***Aims*—To assess the pharmacokinetics of oral, intramuscular, or transdermal hormone replacement in patients with β thalassaemia major.**

***Methods*—Oral (testosterone undecanoate 40 mg) and intramuscular (testosterone propionate 15 mg, phenylpropionate 30 mg, isocaproate 30 mg and decanoate 50 mg) testosterone and transdermal (17β oestradiol 25 μg and 50 μg) oestradiol were evaluated in 21 male (16–29 years) and 11 female (19–26 years) patients with β thalassaemia major and various forms of hypogonadism.**

***Results*—In male patients given oral testosterone, peak testosterone concentrations were observed either two to four hours or seven hours after administration; intramuscular testosterone produced peak values seven days after injection. Transdermal 17β oestradiol given to female patients produced a biphasic pattern with an initial peak concentration occurring at 36 hours and a secondary rise at 84 hours.**

***Conclusions*—The results indicate that oral androgens should be given twice daily in cases of hypogonadism, and where growth is incomplete, lower than recommended doses. If intramuscular testosterone is used, smaller doses of 10–25 mg should be given every one to two weeks. Transdermal administration of 25–50 μg 17β oestradiol generally produces a plasma E2 value in the early to mid-follicular phase range (100–300 pmol/l). This is appropriate in adults but excessive for prepubertal girls. Diffuse iron infiltration of tissues does not seem to interfere with the absorption of androgens and oestrogens from the gut, muscle, or skin.**

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Modern treatment has increased the life expectancy of patients with β thalassaemia major so that more of them reach sexual maturity. In fact, De Sanctis *et al* found that 45% of patients completed puberty spontaneously (personal observations). Many thalassaemic patients, however, still have primary or secondary hypogonadism which manifests as infantilism, pubertal arrest, primary or secondary amenorrhoea in females, or impotence in males.[1–4] For all these conditions, some form of hormone replacement therapy (HRT) is required. Because hypogonadism, once established, is almost certainly irreversible, many thalassaemics will require HRT long term. Such patients are susceptible to chronic active hepatitis,[5 6] impaired glucose tolerance or frank diabetes mellitus,[7 8] thromboembolism,[9] cholelithiasis[10] and cardiomyopathy associated with cardiac failure.[11] Because all these conditions can be adversely affected by hormonal treatment, HRT may have deleterious effects in some patients with thalassaemia major.

To minimise the potential risks of such treatment, excessively high sex hormonal concentrations should be avoided during treatment. Moreover, as linear growth depends on several interacting factors, including sex hormones, a disproportionally high concentration of androgens or oestrogens could adversely affect the final height of thalassaemics receiving HRT.

Little is known about the pharmacokinetics of oral, intramuscular, or transdermal hormone replacement in thalassaemics, or for that matter in healthy adolescents. Hence a study was performed to assess these kinetics in a group of patients with β thalassaemia major.

Methods

Twenty one male patients with β thalassaemia major, aged 16 to 29 years, with varying clinical and hormonal degrees of hypogonadism, were given, at random, either 40 mg testosterone undecanoate (Restandol, Organon Laboratories, Italy) by mouth (n = 13) or 125 mg depot testosterone (Sustanon, Organon Laboratories) intramuscularly (n = 8). The latter contains 15 mg testosterone propionate, 30 mg testosterone phenylpropionate, 30 mg testosterone isocaproate and 50 mg testosterone decanoate.

Two patients had primary hypothyroidism and were receiving L-thyroxine, two had insulin dependent diabetes mellitus, and one had impaired glucose tolerance.

Nineteen patients had liver disease: they either had raised serum glutamyl transpeptide (r GT), raised serum aspartate transaminase (AST) activities, or both, or evidence of chronic hepatitis on liver biopsy.

Eleven female patients with β thalassaemia, aged 19 to 26 years, with arrested puberty (n = 2), primary amenorrhoea (n = 8), or secondary amenorrhoea (n = 1) had their serum oestrone (E1), 17β oestradiol (17βE2)

and oestrone sulphate (E1S) values measured after the application of a skin patch containing oestradiol Estraderm TTS 25 (n = 8), or Estraderm TTS 50 (n = 3) (Ciba-Geigy; Saronno, Varese, Italy). These skin patches delivered 25 μg of 17βE2 transdermally over 24 hours, respectively.

Two patients had primary hypothyroidism and were receiving L-thyroxine; two had chronic liver disease.

The diagnoses of gonadotropin deficiency in males, and of arrested puberty, primary amenorrhoea, and secondary amenorrhoea in females were based on criteria described before.[2 4]

HORMONE ASSAYS

In males blood samples were taken at 0,2,4,7 and 24 hours after oral administration of Restandol, and at 0,7,14,21 and 28 days after Sustanon injection. Serum samples were assayed for total (TT) and free testosterone (FT) concentrations.

In females blood was taken for hormone assay (E1, 17β E2, and E1S) at 0,12,36,60 and 84 hours after application of the patch.

17β E2 values were measured using ether extraction and Sephadex LH20 chromatography, followed by radioimmunoassay (RIA). E1S values were measured as described previously.[4] E1 was determined by an RIA kit (Diagnostics Biochem, Ontario, Canada).

FT values were analysed using the coat-a-count free testosterone procedure and TT values were determined using the Diagnostic Products Corporation (DPC, Los Angeles, California) coat-a-count direct testosterone kit.

Serum ferritin concentrations were measured by immunoradiometric assay (IRMA) in all patients. In thalassaemic males, serum ferritin concentrations varied from 560 to 5220 μg/l (normal values 18–250 μg/l) and in females from 895 to 5075 μg/l (normal values 10–160 μg/l).

The intra-assay coefficients of variation were less than 10% for all of the assays.

Results were expressed as median or mean (SD). Linear regression was used to evaluate correlations between variables.

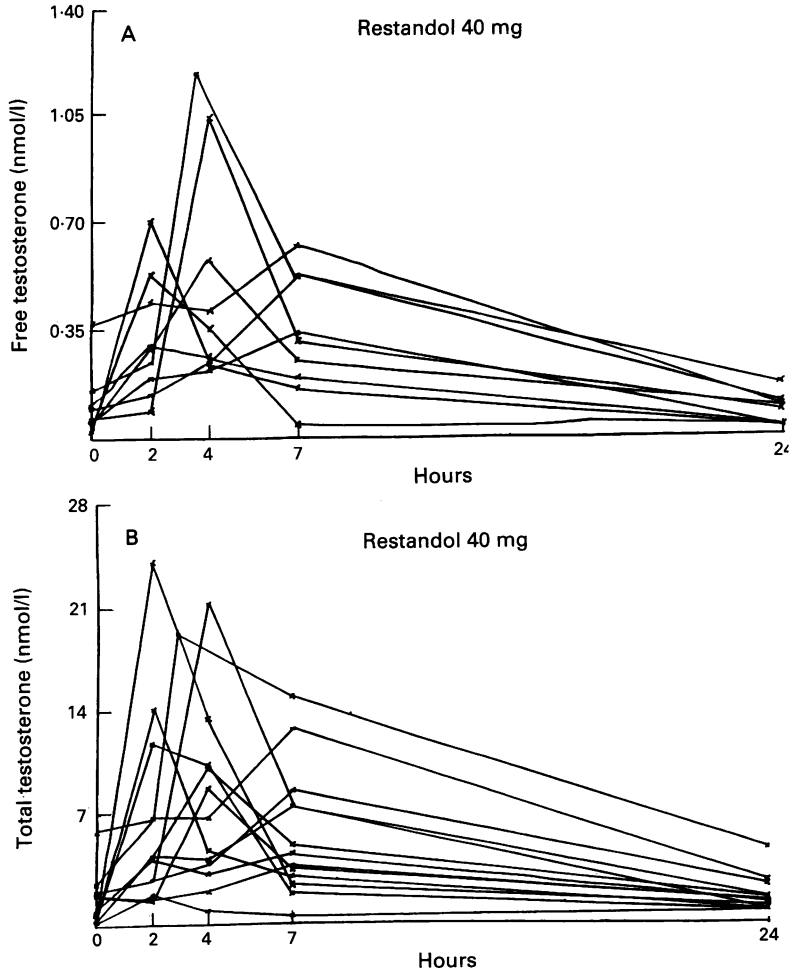

Figure 1 (A) Total serum testosterone concentrations in 13 hypogonadal male thalassaemic patients before and after oral administration of 40 mg of testosterone undecanoate. (B) Free serum testosterone concentrations in nine hypogonadal male thalassaemic patients before and after oral administration of 40 mg of testosterone undecanoate.

Results

TESTOSTERONE UNDECANOATE (RESTANDOL)

Figure 1A illustrates the absorption patterns of TT following the oral administration of 40 mg Restandol to 13 male patients. Two general patterns of TT absorption emerged. The first was characterised by a peak testosterone concentration two to four hours later followed by a rapid reduction in testosterone values by seven hours. The range of peak values was 8·6 to 22·9 nmol/l (median 16·3 nmol/l). The second pattern was characterised by a gradual rise from baseline values to a peak at seven hours. The peak values ranged from 3·6 to 12·4 nmol/l (median 7·9 nmol/l). In most patients testosterone values returned to baseline by 24 hours in both groups (normal basal values: early puberty 2·4 (2) nmol/l, mid-puberty: 11·1 (4·8) nmol/l, late puberty: 13·3 (4·8) nmol/l).

The pattern of FT was evaluated in nine patients and was similar to that observed for TT (fig 1B). The range and median of peak values were 0·2–1·1 nmol/l and 0·5 nmol/l, respectively (normal basal values: early puberty 0·1 (0·09) nmol/l, mid-puberty: 0·5 (0·1) nmol/l, late puberty 0·5 (0·1) nmol/l).

DEPOT TESTOSTERONE (SUSTANON)

In seven out of eight patients given a single intramuscular injection of Sustanon 125 mg peak TT concentrations were achieved by seven days after injection. Thereafter, there was a gradual reduction to baseline in most patients (fig 2A). Peak TT values varied from 7·3 to 32·3 nmol/l (median 19·9 nmol/l). In one patient there was a more gradual absorption, with testosterone values still rising 28 days after injection.

The pattern of FT (fig 2B) resembled quite closely that observed for TT with peak values ranging from 0·2 to 1 nmol/l (median 0·7 nmol/l). In one patient free testosterone concentrations continue to rise until the 21st day after the injection after which a plateau was reached.

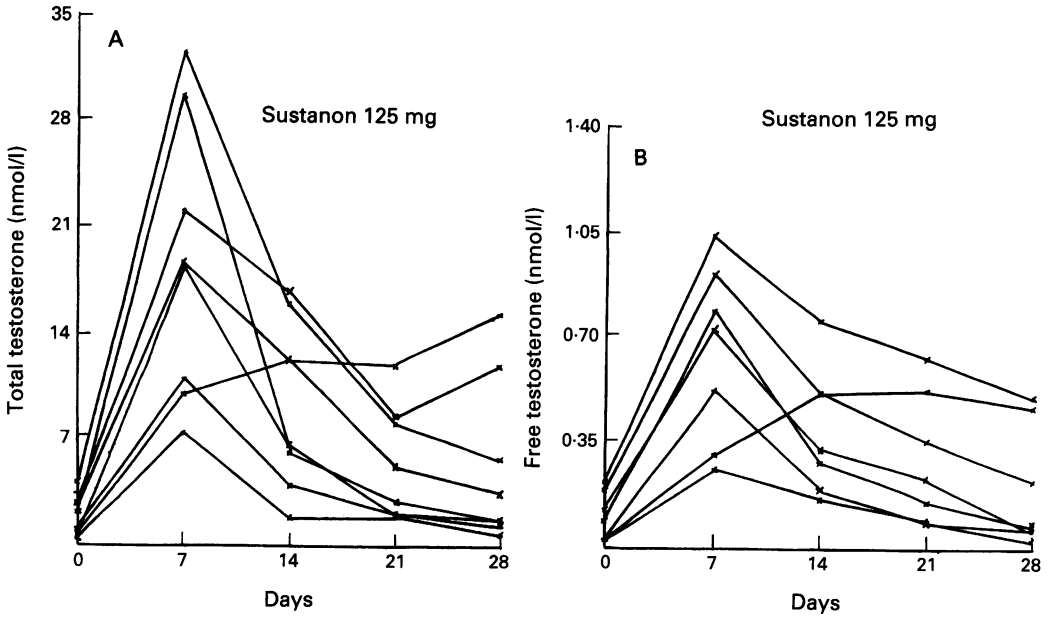

Figure 2 (A) Total serum testosterone concentrations in eight hypogonadal male thalassaemic patients before and after intramuscular injection of 125 mg of depot testosterone. (B) Free serum testosterone concentrations in seven hypogonadal male thalassaemic patients before and after intramuscular injection of 125 mg of depot testosterone.

TRANSDERMAL 17β OESTRADIOL (ESTRADERM TTS)

Fig 3A illustrates the absorption pattern of 17βE2 in the eight patients applying Estraderm TTS 25 and the three patients using Estraderm TTS 50.

17βE2 values peaked at 12 hours in one patient and at 36 hours in the remaining 10 patients. In six patients a secondary rise of 17βE2 occurred at 84 hours, and in two of these the 17βE2 values achieved were greater than those at the initial peak.

Generally, the values achieved during the 84 hour period of study were consistent with those found in the early follicular phase of the menstrual cycle (80–400 pmol/l).

One patient using Estraderm TTS 50 showed no evidence of absorption and this patient had a ferritin concentration of 1305 μg/l.

The absorption curves of the other two patients given Estraderm TTS 50 overlapped with those of the patients given Estraderm TTS 25.

Figs 3B and C show the patterns of E1 and E1S concentrations during the 84 hour period of study. E1 values rose in 10 of the 11 patients after application of the patch, but peak values were scattered between 12 and 60 hours; no consistent pattern of absorption emerged. The one patient whose 17βE2 absorption curve remained flat also showed no increase in E1 values after application of the patch.

Plasma E1S patterns after E2 absorption were also variable and less pronounced. The

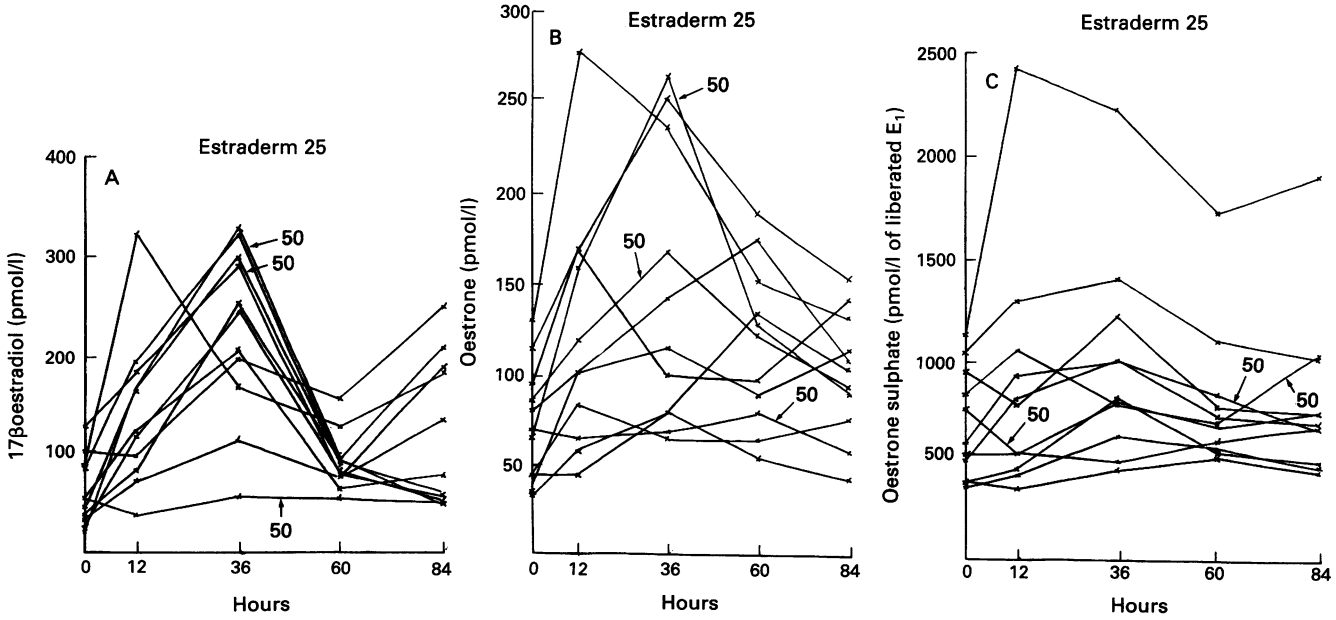

Figure 3(A) Plasma 17β oestradiol concentrations in 11 female thalassaemic patients before and after transdermal β oestradiol 25 μg (eight patients) and 50 μg (three patients). (B) Plasma oestrone concentrations in 11 female thalassaemic patients before and after transdermal β oestradiol 25 μg (eight patients) and 50 μg (three patients). (C) Plasma oestrone sulphate in 11 female thalassaemic patients before and after transdermal β oestradiol 25 μg (eight patients) and 50 μg (three patients).

peak value was greater than twice the baseline value in only three patients and one showed no change at all. Seven patients peaked at 36 hours, two at 12 hours, and one at 60 hours.

Baseline E1 values ranged between 33 and 132 pmol/l (median 84 pmol/l) and peak E1 ranged between 81 and 275 pmol/l (median 170 pmol/l). For E1S, baseline values varied from 369 to 1107 pmol/l (median 799 pmol/l) and peak value ranged between 525 and 2436 pmol/l (median 1091 pmol/l).

Generally, the values achieved were in the normal physiological range for the follicular phase of the menstrual cycle (E1:120–400 pmol/l; E1S 800–1650 pmol/l).

No correlation was observed between the peak values of either oestrogen or androgen and serum ferritin concentration measured at the time of study.

Discussion

Ideally the hormone being replaced during HRT should be delivered reliably and at little inconvenience to the patient. Treatment should provide and maintain a physiological concentration of the deficient hormone. The efficacy of such replacement treatment is usually assessed clinically by the disappearance of acute deficiency symptoms and by the prevention of long term complications. It is equally important, however, to evaluate the pharmacokinetics of the hormone in circulation.

In this respect certain aspects of the current study are worthy of comment.

In the patients treated with Restandol two general patterns of testosterone absorption were observed. No explanation could be found for the different rates of absorption or clearance of testosterone, nor was it possible to predict prospectively or retrospectively from the available data which pattern would emerge in any particular patient. Because the tests were not repeated, it could not be assumed that the pattern was reproducible in the same patient.

In one group of patients there was a definite testosterone peak two to four hours after testosterone undecanoate had been given, while a second group showed a more gradual rise and fall in testosterone values, with peak values at seven hours. In the latter group, however, blood was not taken between seven and 24 hours so one cannot assume that the true testosterone peak occurred at seven hours in this group.

Irrespective of peak testosterone concentration, values were within the normal adult male range. In all cases testosterone values had returned to their pretreatment subnormal baseline values by 24 hours.

Our findings confirm and extend those found in nine hypogonadal non-thalassaemic males studied by Geere *et al.*[12]

These observations allow us to make two recommendations with respect to the administration of Restandol to thalassaemic patients. Firstly, a twice daily dose is more likely to maintain adequate testosterone values throughout the day. Secondly, in those patients whose growth is often retarded and incomplete, the adult male blood testosterone concentrations achieved may be supraphysiological and may hasten epiphyseal fusion, thereby reducing their final height. Such patients should be given smaller doses of Restandol administered in divided daily doses. Where bone epiphyseal fusion is complete, the recommended dose of 40 mg twice or three times a day may safely be given as hormone replacement therapy.

When Sustanon was used, even 125 mg produced supraphysiological peak testosterone concentrations, and two weeks after the injection testosterone values were still greater than 17·3 nmol/l. Hence, especially in peripubertal children with residual growth potential, it may be prudent to give smaller doses of 10 to 25 mg every one to two weeks rather than the higher dose of 250 mg every three to four weeks, as recommended for adults.

FT concentrations should give a more accurate reflection of bioavailable testosterone than TT concentrations, the more so in thalassaemic patients who often have liver disease and, as a result, raised sex hormone binding globulin concentrations.[13 14] Our pharmacokinetic studies showed that FT values mirrored almost identically those of TT; in this respect the FT assays seemed to offer no specific advantage over measurement of TT.

Transdermal testosterone application was not evaluated in this study but should be considered as another possible option.

Two patterns of serum 17βE2 were observed after the application of Estraderm TTS. In most patients serum peak 17βE2 values were recorded 36 hours after the application of the patch. Six out of 11 patients, however, had a secondary rise in 17βE2 concentration at between 60 and 84 hours.

The magnitude of Estraderm TTS absorption was variable but generally the serum 17βE2 values achieved were in the early to mid-follicular phase range, which is perfectly appropriate for hormone replacement therapy in adults but may be excessive for prepubertal girls.

Illig *et al*, using 5–10 μg Estraderm TTS, achieved reasonable growth stimulation and concomitant pubertal development in patients with Turner syndrome, suggesting that these lower doses are more appropriate for prepubertal girls with unfused epiphyses.[15] Those who manage patients with β thalassaemia major will be aware of the precarious nature of the disease.

Because most thalassaemic patients have liver disease and iron infiltration of all their tissues,[17] it could not be assumed that the pharmacokinetics of the sex hormones studied would be the same as in non-thalassaemic subjects. In any event such studies in adolescent and young adults have not been published. In this respect the current study provides much useful information. Diffuse iron infiltration of tissues does not seem to

interfere with the absorption of androgens and oestrogens from the gut, muscle, or skin. The one female patient whose 17βE2 remained unchanged after the application of Estroderm TTS did not have evidence of heavy iron overload.

A second lesson learned from this study is that, while the hormone doses used were appropriate for adult hormone replacement therapy, smaller doses may be needed to achieve the physiological concentration of sex hormone required to promote normal puberty and to safeguard growth in adolescence. It still needs to be shown, however, that the smaller doses recommended in this paper will achieve the desired clinical effects in thalassaemic patients.

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