Oxandrolone in growth hormone-treated girls with Turner syndrome

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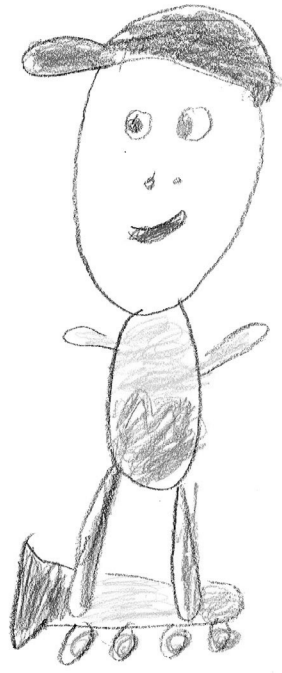
General discussion and conclusions



Effect of oxandrolone on height during therapy, adult height gain, and duration of growth hormone therapy

This thesis describes the results of the first randomized, double-blind, placebo-controlled study on the question which has remained unanswered up to now: whether growth hormone (GH)-treated girls with Turner syndrome (TS) would profit from oxandrolone (Ox) therapy, and if so, which Ox dosage should be given.

Several potential beneficial effects of the addition of Ox to GH were investigated, including an increase in height during therapy, an increase in adult height gain, and a shorter duration of GH therapy, which would imply fewer subcutaneous GH injections and less GH-associated costs (Table 1). With respect to these endpoints, we can now conclude the following. The addition of either Ox 0.03 or 0.06 mg/kg/day results in a significant increase in height during therapy. Whereas mean height during therapy remained below the normal range for Dutch healthy girls in the group using GH+Pl, it increased to values well within the normal range on either GH+Ox 0.03 or GH+Ox 0.06. This means that in the psychological vulnerable time of childhood and puberty, the girls had a height that was comparable with girls of their age. The differences between the groups however decreased before reaching adult height. Partly due to the increase in bone age maturation with increasing Ox dosages, adult height was reached at a younger age on both Ox dosages than on Pl. Consequently, GH+Ox 0.06 did not significantly increase adult height gain. The finding that Ox 0.06 does not increase adult height gain was recently confirmed by the preliminary data of a placebo-controlled study coordinated by Ross and colleagues.[1] In contrast, the growth-promoting effect of GH+Ox 0.03 outweighed the increase in bone maturation, resulting in an increase in adult height gain of 2.3 cm (95% CI, 0.4 to 4.2 cm) in the intention-to-treat analysis, and 3.1 cm (95% CI, 0.5 to 5.6 cm) in the per-protocol analysis compared with GH+Pl. The effect was similar in the three age groups.

Because of the increase in bone age maturation, the duration of GH therapy was approximately 5 months shorter on GH+Ox 0.03, and 9.5 months shorter on GH+Ox 0.06 (when corrected for bone age at starting GH). As a result, the cumulative costs of GH were respectively 10,100 and 13,500 euro less than the mean cumulative costs of 161,200 euro on GH+Pl.

Table 1. Schematic representation of probable benefits and harms of GH+Ox 0.03 and GH+Ox 0.06 versus GH+Pl.

	GH+Ox 0.03	**GH+Ox 0.06**
Benefits	Increases adult height gain: - intention-to-treat analysis: mean±SD, 9.5±4.7 vs. 7.2±4.0 cm on GH+Pl - per-protocol analysis: 9.8±4.9 vs. 6.8±4.4 cm on GH+Pl	
	Increases height during therapy	Increases height during therapy
	Tended to shorten the duration of GH therapy (P=0.06): - somewhat less costs - less subcutaneous injections	Shortens the duration of GH therapy: - less costs - less subcutaneous injections
		Decreases systolic blood pressure
	Lowers relatively high voices towards a normal voice pitch	
	Transiently decreases HbA1c and fasting glucose levels	Transiently decreases HbA1c and fasting glucose levels
	Somewhat reduces subcutaneous fat mass	Reduces subcutaneous fat mass
	Decreases pelvic width compared with height	Tends to decrease pelvic width compared with height
	Theoretically may cause a more physiological androgen exposure	
Harms	Decelerates breast development	Decelerates breast development
		Results in subjective virilizing adverse events*
		Results in objective voice lowering, with some girls obtaining voice frequencies below -2 SDS
	Increases muscularity	Increases muscularity
		Increases length of the spine compared with height
		Tends to increase shoulder width compared with height

* Subjective virilizing adverse events consist of subjective voice deepening, clitoral enlargement, and/or an increase in body hair.

Safety parameters

Also several safety parameters were incorporated in the study (Table 1). First, pubertal maturation was influenced by the addition of Ox. Pubic hair stage SDS increased significantly more on GH+Ox 0.03 and 0.06 than on GH+Pl during the first two years of Ox/Pl. Since pubic hair stage was delayed compared with healthy girls both before and after GH+Ox/Pl therapy, we do not consider this a clinically relevant adverse effect. It might even reflect that, especially during Ox 0.03 therapy, androgen levels were substituted towards more physiologic levels. Of some concern was the finding that the addition of Ox to GH slowed breast development. Although breast stage SDS caught up after discontinuing GH+Ox and increasing estrogen dosages, it was still lower on GH+Ox 0.03 than on GH+Pl at the end of the follow-up period: the median Tanner breast stage was 4 (range 2-5) in group GH+Ox 0.03 versus a median of 5 (range 4-5) in group GH+Pl. It is unclear why the addition of GH+Ox 0.03 delayed breast development more than GH+Ox 0.06. A possible explanation is that girls on GH+Ox 0.06 discontinued Ox more frequently preliminarily, and that they used Ox for a shorter duration than girls on GH+Ox 0.03, because they reached adult height at a younger age. Because breast development is generally agreed to be very important for the psychosocial well-being of girls with TS,[2] this may become an argument for the patients either not to use or to discontinue Ox.

Second, virilizing adverse events consisting of voice deepening, clitoral enlargement, and/or hirsutism were studied. Forty-two percent of the patients on GH+Ox 0.06 reported virilization, and about half of these patients decided to discontinue Ox for that reason. Girls on GH+Ox 0.03 also reported somewhat more virilizing adverse events than girls on GH+Pl, but this difference did not reach statistical significance. Voice recordings, performed to objectify virilization, indeed showed that Ox 0.03 and 0.06 resulted in voice deepening in a dose-dependent way. The relatively high-pitched voices of the girls before therapy remained relatively high-pitched on GH+Pl therapy, but became comparable with those of healthy girls on either GH+Ox 0.03 or GH+Ox 0.06. Although voice frequency remained within the normal range in most girls, it occasionally became lower than -2 SDS, especially on GH+Ox 0.06 mg/kg/day. A significantly high voice frequency may be as undesirable

as a significantly low voice frequency. This may especially be true for patients with TS, who are often perceived as younger than their actual age.[3] In this respect, the voice lowering in patients treated with GH+Ox 0.03, which results in a mean adult voice frequency close to the mean of the normal population, may even be regarded favorable for part of the girls. In this context it is relevant to note that hirsutism and clitoromegaly seem to regress after discontinuing Ox,[4, 5] whereas voice deepening appears irreversible.[6]

Third, IGF-I levels were more frequently increased on GH+Ox than on GH+Pl, whereas the increase in IGF-I levels and IGF-I/IGFBP-3 ratio was not significantly different between the dosage groups. The finding that IGF-I levels were more frequently increased on GH+Ox than on GH+Pl may possibly reflect the finding that IGF-I levels were coincidentally already higher before starting Ox in groups GH+Ox 0.03 and GH+Ox 0.06. Previous studies also showed conflicting results regarding the effect of Ox on IGF-I levels and IGF-I/IGFBP-3 ratio.[7, 8] Unfortunately, our study was not conclusive on this point.

Fourth, metabolic parameters including liver enzymes, blood pressure, and glucose metabolism were studied. Although in the literature, Ox at dosages ≥ 0.1 mg/kg/day was found to elevate liver enzymes in non-TS patients,[9] no such effect was found at the dosages we studied. The addition of Ox did not increase diastolic blood pressure, whereas systolic blood pressure even tended to decrease on GH+Ox 0.06 versus GH+Pl. Insulin sensitivity was affected by the addition of neither Ox 0.03 nor 0.06. However, one girl, who already had an impaired glucose tolerance at baseline, had impaired glucose tolerance and an elevated HbA1c (7.7%) after two years of GH+Ox 0.03 therapy. She therefore discontinued GH+Ox, after which HbA1c and glucose levels returned to normal. The HbA1c levels of all other girls remained normal, and none of the girls developed diabetes mellitus type 1 or 2. Fasting glucose levels (and HbA1c levels in the first two years of Ox/Pl therapy) even decreased on GH+Ox compared with GH+Pl, possibly due to an Ox-induced resistance to glucagon.[10-12] Reassuring was the finding that none of the patients developed fasting glucose levels below 2.7 mmol/l. Because fasting glucose levels were reported to be slightly but significantly higher in women with TS than in age-matched control women,[13] the Ox-induced lowering of the fasting glucose might be regarded a favorable effect of Ox.

Fifth, we found that Ox 0.06 reduced subcutaneous fat mass, and both Ox dosages increased muscle mass, resulting in a fat mass that was lower and a muscle mass that was higher than in healthy girls, respectively. The finding that an increase in muscularity was noted by twelve patients implies that the change in muscle mass was clinically noticeable. The increased muscularity was however never mentioned as one of the reasons to discontinue Ox, suggesting that these changes were not so inconvenient that patients decided to give up possible extra centimeters of height. Furthermore, muscle mass decreased after discontinuing GH+Ox, reflecting the reversibility of the effect of GH+Ox. Because fat mass is generally greater in girls and women with TS than in controls,[13] we think that the Ox-induced lowering of subcutaneous fat mass should be regarded as a positive effect.

Furthermore, body proportions were investigated. Compared with GH+Pl, GH+Ox 0.06 increased sitting height, and tended to increase biacromial distance and decrease biiliacal distance, while GH+Ox 0.03 significantly decreased biiliacal distance compared with height. Two out of five patients mentioned the increase in shoulder and/or thorax width as one of the reasons to discontinue Ox prematurely. Especially because the increase in biacromial distance compared with height is irreversible, we consider this a notable adverse effect of Ox 0.06. Ox 0.06 furthermore tended to increase the length of the spine compared with the legs, which may also be regarded unfavorable. On the contrary, the decrease in biiliacal distance on Ox 0.03 may be interpreted as a favorable effect, because this results in a less disproportioned growth with less broad hips.

Finally, we found that neither Ox 0.03 nor Ox 0.06 significantly affected behavior, aggression, romantic and sexual interest, mood, and gender role in GH-treated girls with TS. No increase in aggression proneness and feelings was found, which confirms the conviction that androgens increase this characteristic when given at very high doses only.[14] Furthermore, no effect of Ox on romantic and sexual interest was found. Although testosterone appears to improve sexual desire in adult women with TS [15], testosterone levels in adult patients were not correlated with any aspect of sexual function [16], confirming that androgens in the low physiological range have little impact on sexuality.[17] In addition, we did not find an effect of Ox on positive or negative mood variables. A previous pilot study in adult women with TS found

that testosterone therapy increased quality of life and well-being,[15] possibly by compensating the androgenic insufficiency in TS. We did not find an effect of Ox on gender role preferences, which is in line with the expectation that gender role is not so much influenced by postnatal androgen therapy.[18]

Implications

Because of several reasons, we discourage the use of GH+Ox 0.06 mg/kg/day. Although it increases height during therapy and shortens the duration of GH therapy, it does not significantly increase adult height gain, and has several adverse effects (Table 1). These include a deceleration of breast development, irreversible voice deepening in some patients, an increase in muscularity and the length of the spine compared with the height, and a tendency to increase shoulder width. Because of virilization several girls on Ox 0.06 decided to discontinue Ox preliminary.

In contrast, the addition of Ox 0.03 mg/kg/day to GH increases height during therapy, somewhat shortens the duration of GH therapy, and modestly increases adult height gain. It has a fairly good safety profile, except for some deceleration in breast development, and possibly some mild and transient virilizing side effects. In patients considering the small deceleration of breast development less important than the increment in height gain, Ox 0.03 mg/kg/day may be added to GH from the age of eight years to increase height by a mean of 2.3 to 3.1 cm.

Methodological considerations

This study is the first, and to the best of our knowledge only study to assess the effect of Ox at a dosage as low as 0.03 mg/kg/day. It includes a large population of girls with TS between the age of 2 to 16 years old, which has the advantage that we now know that the effect of Ox was similar in both relatively young (8-11 years at starting Ox) and older (12-15 years at starting Ox) patients. The study furthermore assesses a wide range of possible adverse effects. All variables were assessed longitudinally by two trained observers during the total study period, and all analyses were performed by one investigator.

The analyses on efficacy were performed according to the intention to treat principle: we analyzed all patients, including those who violated the protocol. According to the consort statement, an intention-to-treat analysis prevents bias caused by the loss of participants (www.consort-statement.org). A common modification of the intention to treat analysis (including only patients who take at least one dose of the study medication) was used to prevent under-estimation of the possible adverse effects. Four patients were lost to follow-up and were excluded because we were unable to obtain their data. A further nine had yet to reach adult height and were therefore not included. Because these patients were evenly distributed across the three dosage groups, and their baseline characteristics were similar to those of the analyzed patients, we consider the conclusions of our study generalizable to other girls with TS in whom Ox therapy may be considered.

Our study has some limitations. First, it would have been better to randomize the patients at starting Ox/Pl, rather than at starting GH. In that case, patients who refused to start Ox/Pl would have been excluded from randomization. Second, no standardized scoring system was used in the assessment of the reported subjective virilizing adverse events. Consequently, the reported virilization may underestimate its actual occurrence. Because we were unable to compare the girls with healthy girls in puberty, it is also unclear whether the reported subjective virilization should be regarded as genuine virilization or a normalization from an androgen-insufficient state. The relatively great number of patients that discontinued Ox 0.06 due to virilization, as well as the objectively measured voice lowering, however, suggest that this dosage indeed results in virilization. Third, not all voice recordings were performed or analyzed due to logistic and technical problems. In our view, our findings are however still valid because voice recordings were missing at random and because all available voice recordings were analyzed using repeated measurements (a method that takes into account missing data). Finally, we did not assess possible effects of the addition of Ox on quality of life and well-being, lengths and widths of the hands and feet, and on cardiovascular parameters. With respect to quality of life and well-being, we hypothesize that the observed delay in breast development may negatively affect these parameters, whereas the increase in height during therapy

as well as the decrease in duration of GH therapy (i.e. less subcutaneous injections) may have some positive effects. Compensating the androgenic insufficiency[19, 20] in TS may also have a more direct positive psychological effect, similar to the effect on well-being and quality of life observed in androgen-treated adult patients with TS.[15] With respect to hand and foot width, a previous study showed that Ox therapy resulted in increased hand and foot widths in the first two years (at a dose of 0.1 mg/kg/day), whereas it did not significantly increase hand and foot length compared with height.[21] Whether Ox 0.06 and 0.03 may have a similar (though smaller) effect on hand and foot width is unknown, as far as we are aware. With regard to cardiovascular parameters, a previous study in patients with TS suggested a positive role of Ox on cholesterol levels,[5] whereas another study found that HDL levels were slightly lower, and cholesterol levels were similar on GH+Ox 0.06 versus GH+Pl.[1] To our knowledge, no data have been reported on the effect of Ox on cardiovascular dimensions and function.

Future research

Now we have learned that the addition of low-dose Ox increases height gain in GH-treated girls with TS, some interesting questions need to be addressed. Optimizing the age at which Ox is started, as well as elucidating the most advantageous dosage will help optimizing adult height gain as well as controlling the frequency of adverse events. Alongside, long-term consequences need to be examined.

Our finding that adult height gain on Ox 0.03 versus Pl was not significantly greater in age groups 1 (Ox started at age 8) and 2 (Ox started at age 8-11) than in age group 3 (Ox started at age 12-16) suggests that there is no advantage of moving the Ox starting age to a relatively young age. A previous study showed that bone age advanced inappropriately in girls treated before a bone age of eight years.[22] Considering that bone age maturation is usually delayed in TS, Ox was started at a relatively young age in our study. Furthermore, in the literature androgen levels in girls with TS were found to be lower than in control girls from the age of ten to thirteen years onwards,[19] suggesting that this may be a more physiological age range to start Ox. With respect to the disadvantage of Ox in decelerating breast stage development, it will be interesting to study height gain and breast development if Ox

is started after a period of gradual age-appropriate estrogen replacement. In a study by Ross *et al.*, oral ethinyl estradiol was given (in addition to GH) at a dosage of 25 ng/kg/day at the age of five to eight years, 50 ng/kg/day at the age of 8 to 12 years, and 100 ng/kg/day at the age of 12 to 14 years, after which dosages were doubled yearly to menarche.[23] This regimen accelerated breast development from the age of 9 to 12 years and resulted in a better adult height than GH plus placebo rather than estrogens.[23, 24] If Ox would be subsequently started at the age of 12 years, breast development would already have been started in most girls.

Current data suggest that the optimal Ox dosage with respect to height gain seems to lie between 0.03 and 0.04 mg/kg/day, bearing in mind though that the expected good results on Ox 0.05 mg/kg/day found by Donaldson and colleagues were obtained using a maximum daily dose of 2.5 mg.[25] Rather than using a maximum dose as a strategy to prevent too high dosages in overweight patients, dosages may be calculated per m^2 body surface area. Preliminary data obtained by our study group found that GH dosing by body surface area lead to stable IGF-I SDS levels, whereas GH dosing by body weight lead to relatively low doses in young or lean children, and high doses in older or overweight children. This suggested that body surface area may be superior to body weight for scaling GH dosage in children.[26] Possibly, the same could be true for Ox therapy. It would however be even more interesting to assess the effect of Ox at physiological androgen dosages, which would imply that Ox dosages would increase with advancing age. This would imply that patients with mosaic karyotypes and/or spontaneously developing puberty would be treated with lower dosages, since endogenous androgen concentrations were found to be higher in mosaic karyotypes than in 45,X karyotypes.[19] The next step would be dosage individualization, with dosages being based on the level of androgen insufficiency in each patient. Apart from a possibly better height gain due to a decrease in bone age maturation, this strategy might result in less virilizing adverse events.

In the coming years, we expect the results from *'the Turner Oxandrolone Follow-up Study*', the follow-up study of the trial described in this thesis. Although the original study included a follow-up period of 1.9±0.8 years after discontinuation of GH+Ox/Pl, the longer follow-up will provide data on long-term efficacy and safety, as well as data on neuropsychological functioning and quality of life parameters, which were not included in *the Dutch Turner Oxandrolone Study*. Also a genetic follow-up study will be performed.

Apart from the above questions directly associated with the clinical recommendations, further research is also needed on the mechanisms involving the effects of Ox on the various efficacy and safety outcome measures. In chapter two we referred to a recent report that showed that bone growth in vitro was not influenced by Ox, suggesting that Ox may influence the growth plate mainly in an indirect way.[27] We suggested that Ox may increase growth by increasing IGF-I (presumably by increasing insulin-induced hepatic GH receptors),[28] by suppressing IGFBP-I (an inhibitor of IGF-I),[28] and/or by increasing free estrogen levels due to an Ox-induced decrease in SHBG.[28, 29] Elucidating the exact mechanism of actions of Ox would possibly help optimizing clinical care involving Ox therapy in patients with TS.

Conclusions

We conclude that in GH-treated girls with TS, the conventional Ox dosage (0.06 mg/kg/day) should not be used because of its limited efficacy and virilizing capacity. In contrast, the addition of Ox at a dosage of 0.03 mg/kg/day starting between 8-15 years increases height during therapy, modestly increases adult height gain and has a fairly good safety profile, except for a small deceleration in breast development. In patients considering this deceleration less important than the increment in height gain, we suggest to add Ox 0.03 mg/kg/day to GH to increase height. Optimizing the age at which Ox is started, as well as elucidating its most advantageous dosage will help optimizing adult height gain as well as controlling the frequency of adverse events. *The Dutch Turner Oxandrolone Follow-up study* will provide the long-term follow-up data of the girls and women who took part of the study described in this thesis.

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