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# Antiandrogenic treatment of benign prostatic hyperplasia: a placebo controlled trial

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**Summary.** In a randomized triple-blind multicentre study, injections with the anti-androgenic agent oxendolone were compared with placebo in the treatment of benign prostatic hyperplasia. Thirty patients were treated with weekly injections of oxendolone 200 mg during a 3 months' period, and 30 patients were allocated to placebo treatment. During oxendolone treatment the maximum urinary flow rate increased statistically significantly (from 6.8 ml/s to 8.2 ml/s). However compared to placebo, the oxendolone effect was statistically insignificant. A slight but statistically significant improvement of the symptoms "sensation of retention", "urgency" and "frequency", was observed following oxendolone treatment, but an almost identical effect was seen in the placebo group. Following either treatment no change was observed in the residual urine volumes, in prostatic volume as measured by transrectal ultrasonotomography, or in any other therapeutic parameters. Conservative treatment of benign prostatic hyperplasia with the antiandrogen oxendolone in a dose of 200 mg a week cannot be recommended for clinical use.

**Key words:** Benign prostatic hyperplasia – Prostatic hypertrophy – Medical treatment

## Introduction

Benign prostatic hyperplasia (BPH) is a major problem in elderly males with about 60% over the age of fifty developing clinical symptoms and about 10 to 30% requiring surgical treatment.

Although excellent results are obtained from surgical treatment of BPH, there still remains a need for conservative treatment of the disease, especially in patients with concomitant serious diseases.

The etiology of BPH has not yet been clarified, but several studies have showed a strong influence of androgens on prostatic growth [14, 16].

Oxendolone (16 beta-ethyl-17 beta-hydroxy-4estren-3-one) is a derivate of 19-Nortestosterone with a strong antiandrogenic activity. Experimental studies have shown the antiandrogenic effect to be due to a dose dependent inhibition of the testosterone uptake in the prostate [12], an inhibition of the testosterone-5-alpha-reductase in the prostatic cells [10], and a competitive inhibition of the formation of the dehydrotestosterone-receptor complex [13]. The drug has minor hormonal activity and does not involve hypophyseal mechanisms, and thus universal endocrine effects are avoided [5].

A promising effect of oxendolone in the treatment of BPH has been reported in previous studies [8, 11, 15].

To study the effect of oxendolone in treatment of BPH, we conducted a prospective placebo controlled study.

## Material and methods

A triple blind, placebo controlled study on BPH patients was performed from October 1982 to December 1984 at the departments of urology in Gentofte Hospital Denmark and in Ørebro Hospital Sweden.

Sixty-two patients (31 from each Hospital) needing surgical treatment due to BPH entered the study.

Excluded from the study were:

- patients previously treated for BPH,
- patients with a peak flow above 10 ml/s,
- patients with acute urinary retention,
- patients with indwelling urethral catheters,
- patients with increased plasma-creatinine levels,
- patients with neurological or psychological diseases,
- patients suspected of detrusor – bladder neck dyssynergia,
- patients with other pharmacological treatment influencing the bladder-urethra function,

- patients with hematological or liver diseases,
- patients with suspected prostatic cancer, hematuria, prostatitis, or diagnosed urinary calculi.

Bacteriuria was treated prior to the study.

Two of the 62 patients were excluded from the study (in one patient a urethral stricture was diagnosed during subsequent operation, and one patient dropped out before receiving any treatment).

The mean age of the remaining 60 patients was 69 years (range 56–88 years). The mean patient age at Gentofte hospital was statistically significantly higher (72 years) than at Ørebro (66 years). Except for age the patients at the two centres were comparable.

There were no differences in age, height, weight, severity of prostatic symptoms, and duration of symptoms between the placebo group and the oxendolone group.

Thirty patients (15 from each hospital) were allocated to weekly intramuscular injections with oxendolone 200 mg for 12 consecutive weeks, and 30 patients to placebo injections. The nurses administering the injections were aware of the coding sequence, but otherwise not involved in the study.

Clinical assessments of the therapeutic effect on the basis of objective findings and subjective symptoms were registered before and after 5, 9 and 13 weeks of treatment.

From interviews the prostatic symptoms "sensation of retention", "weak stream", "urgency" and "incontinence" were graded on a scale from 0–3, and the patients were questioned if they had "difficulty in starting" or "post micturition dribbling". Flowmetry was performed at every control, and the patients listed the number of voiding events on an micturition-chart for a three-day period before each control. Before and after treatment the residual uringe volume were measured by ultrasound, and at one centre (Ørebro) the prostatic volume was assessed by means of transrectal ultrasonic investigation. Additionally, the sexual function was assessed by interviews.

The overall therapeutic effect of the treatment was assessed as follows: the symptoms and findings were divided into 2 groups.

- Group A consisted of the *objective* findings: measurements of 1) the urinary flow rate and 2) the residual urine volume.
- Group B consisted of the *subjective* symptoms subdivided into 1) irritative symptoms (frequency, nocturia and urgency) and 2) obstructive symptoms (weak stream, sensation of retention).

To fulfil the criteria for successful treatment, the patients should show improvements in at least one of the subgroups of both group A and B.

Following the treatment the patients were asked if they still wanted an operation for BPH. In case of operation the removed prostatic tissue was histologically examined.

Side effects were recorded, and blood samples for hematology, renal and liver function were obtained pre-, per- and post-therapy.

### *Ethical considerations*

The study was done in accordance with the Helsinki Declaration of. Informed consent was obtained from all the patients, and the study was approved by the National Health Authorities and the local ethical committees.

### *Statistical analysis*

Analyses of any differences between baseline score and later scores for evaluating therapeutic effect for both treated groups, were made by using Wilcoxon matched-pairs signed-ranks test. Analyses of any differences between the two treatment groups were made by using Mann-Whitney U test. Analyses of anamestic data, difficulty in starting, and postvoiding dribbling were evaluated by using a Chi square-test or a Fisher exact probability test. $P<0.05$ was considered the level of significance.

## Results

The effect of treatment on the *objective* parameters; maximum flow rate, residual urine volume and prostatic volume are given in Table 1.

Two patients were not assessed at status week 13. In one patient the oxendolone treatment was stopped at week 11 due to adverse reactions, and one patient in the placebo group was operated at week 12 due to acute urinary retention.

In the oxendolone group the maximum flow rate increased statistically significantly at week 13. Also in the placebo group the flow rate increased during treatment, and the improvement was statistically significant at week 5. Comparison of maximum flow rates in the two groups failed to show any differences between oxendolone and placebo treatment at any status week.

The residual urine volume decreased (Table 1) insignificantly during oxendolone treatment, whereas a small rise of 12 ml was found in the placebo group. Comparison of residual volumes in the two groups did not show any differences at baseline or following treatment.

A small but insignificant decrease in prostatic volume was observed following oxendolone treatment.

The therapeutic effect on the *subjective* symptoms either obstructive or irritative are given in Tables 2 and 3.

In both groups the patients stated an improvement of their urinary stream during treatment, but the improvements were statistitically insignificant and were comparable in the two groups.

A significant reduction in the average score for the symptoms "urgency" (Table 3) and "sensation of retention" (Table 2) was observed following treatment with oxendolone as well as placebo. The improvements, however, were very similar in the groups, and no statistically significant differences were seen.

The frequency of micturition was reduced in both groups during treatment (Table 3). The decrease in frequency during 24 h was statistically significant in the placebo group at week 9, and at week 13 in the oxendolone group. However, comparisons of the two groups did not show any difference at any status week. The patients treated with placebo had a significant reduction in nocturia at week 9, but again no differences were seen between the groups.

**Table 1.** The effect on objective parameters

| Status week | Average values | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Max. flow rate | | | | Residual urine volume | | | | Prostatic volume | | | |
| | Oxendolone | | Placebo | | Oxendolone | | Placebo | | Oxendolone | | Placebo | |
| | *n* | ml/s | *n* | ml/s | *n* | ml | *n* | ml | *n* | ccm | *n* | ccm |
| 0 | 30 | 6.8 | 30 | 7.0 | 29 | 155 | 27 | 134 | 15 | 48 | 15 | 54 |
| 5 | 30 | 6.7 | 30 | 8.0* | – | | | – | | | | |
| 9 | 30 | 7.0 | 30 | 8.1 | – | | | – | | | | |
| 13 | 29 | 8.2* | 29 | 8.0 | 29 | 137 | 27 | 146 | 15 | 47 | 15 | 53 |

* $P<0,05$ vs. baseline

**Table 2.** The effect of treatment on obstructive symptoms

| Status week | Symptoms | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Weak stream | | | | Sensation of retention | | | |
| | Oxendolone | | Placebo | | Oxendolone | | Placebo | |
| | *n* | Score | *n* | Score | *n* | Score | *n* | Score |
| 0 | 30 | 1.4 | 30 | 1.4 | 30 | 0.8 | 30 | 0.9 |
| 5 | 30 | 1.3 | 30 | 1.2 | 30 | 0.6 | 30 | 0.7* |
| 9 | 30 | 1.3 | 30 | 1.2 | 30 | 0.5 | 30 | 0.7 |
| 13 | 29 | 1.1* | 29 | 1.2 | 29 | 0.5* | 29 | 0.7* |

score = average values of symptoms graded from 0–3
* $P<0,05$ vs. baseline

**Table 3.** The effect of treatment on irritative symptoms

| Status week | Symptoms | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Frequency | | | | Nocturia | | | | Urgency | | | |
| | Oxendolone | | Placebo | | Oxendolone | | Placebo | | Oxendolone | | Placebo | |
| | *n* | Voidings | *n* | Voidings | *n* | Voidings | *n* | Voidings | *n* | Score | *n* | Score |
| 0 | 30 | 7.3 | 30 | 7.2 | 30 | 1.8 | 30 | 1.9 | 30 | 1.2 | 30 | 1.4 |
| 5 | 30 | 7.1 | 30 | 7.0 | 30 | 1.6 | 30 | 1.5 | 30 | 1.1 | 30 | 1.2 |
| 9 | 30 | 6.7 | 30 | 6.6* | 30 | 1.7 | 30 | 1.5* | 30 | 0.9 | 30 | 1.1 |
| 13 | 29 | 6.6* | 29 | 6.5 | 29 | 1.6 | 29 | 1.4 | 29 | 0.9* | 29 | 1.0* |

score = average values of symptoms graded from 0–3
* $P<0,05$ vs. baseline

Twenty patients in the oxendolone group, and 19 in the placebo group claimed of "hesitancy" before treatment. No improvement was observed during treatment. Following treatment 14 patients in the oxendolone group and 15 patients in the placebo group were still hampered by that symptom.

During treatment with oxendolone the number of patients reporting "postvoiding dribbling" was redu-

ced from 18 to 11. In the placebo group the number was reduced from 17 to 8. This difference was statistically insignificant.

With an average score of 0.13 in the oxendolone group and 0.23 in the placebo group incontinence was found to be a minor problem before treatment. Following treatment the score had decreased in the oxendolone group to 0.07 and in the placebo group to 0.17. This reduction was not significant, and again no statistically significant differences were found between the groups.

Excluding the patient in the oxendolone group in which the treatment was stopped at week 11 due to an adverse reaction, 59 patients were evaluable concerning the overall clinical effect. No difference was found between the groups (eleven of 29 patients in the oxendolone group, and 12 of 30 patients in the placebo group fulfilled our criteria for succesful treatment).

Only a few unwanted reactions were observed during oxendolone treatment. In one patient the treatment was stopped due to the development of arthralgia. The symptoms ceased after a few weeks, and the relationship between these symptoms and oxendolone was uncertain.

No patient treated with placebo, but fifteen patients treated with oxendolone claimed short-lasting pain at the site of injection.

Neither oxendolone nor placebo treatment had any influence on sexual parameters: frequency of coitus, erecton or ejaculation.

A slight but significant decrease in the average concentration of hemoglobin was found after treatment with oxendolone, and in one patient a minor increase in the number of platelets was recorded. Otherwise no changes were found in the blood samples during treatment.

## Discussion

Several studies of BPH based on the principle of inhibiting the androgenic influence on the prostatic gland have been published without reporting any definite success of treatment [1, 4, 6, 9].

Promising clinical results have been reported from several recent Japanese studies using a new antiandrogenic drug, oxendolone in a weekly dose of 200 mg i. m. [8, 11, 15]. The design of these studies were with few exceptions non-randomized and open, and in no case a placebo treatment group was included.

BPH is a disease with a spontaneous improvement as high as 60–65% [1, 2]. Considerable placebo response must therefore be expected in any treatment of BPH, and this was the reason for designing our study as a randomized comparative study including placebo. As an identically looking placebo solution was not available a triple-blind design was chosen, meaning that only the nurses administering the drugs were aware of the coding sequence. The blindness was kept during the entire study for the patients as well as for the evaluating physicians, and in this way the study may be regarded as a double-blind study.

Following oxendolone treatment we observed a statistically significant improvement of the symptoms "sensation of retention", "urgency" and "frequency", but an almost identical response was seen in the placebo group, and no statistical significances between the 2 groups were found.

In both active and placebo groups an objective improvement was documented in bladder function, but again no statistically significant difference was observed. The maximum flow rate is influenced by the volume voided and the age. A method for adjusting maximum urinary flow rate for age and volume voided has been proposed by Drach et al. [3]. Adjusting our data by this method we still found a non-significant difference.

To evaluate any treatment effect on the size of the prostate we used transrectal ultrasonotomography due to the well known inaccuracy in assessments from rectal digital palpation [7]. In contrast to our study Saitoh et al. [8] found a reduction of the prostatic volume in 47% of the patients, but their study only included 17 patients. We also failed to demonstrate any significant change in the residual urine volume during treatment.

Shida et al. [11] reported in their study a microscopically evident contraction of nodular hyperplasia of the prostate following oxendolone treatment. As a result of the lack of therapeutic response the majority of the patients in our study were operated soon after the trial period. Prostatic tissues from the operated patients were investigated histologically by a pathologist unaware of the preceding treatment. No differences in the histological pattern were found between the groups.

Using our data from the overall clinical effect, and requiring a minimum difference of 25% in response between oxendolone and placebo treatment, the probability for overlooking a 25% difference was calculated to 4%. A type 2 error (i. e. the risk of a false-negative result) of 4% was considered very low and conclusive.

## Conclusion

This study failed to support the hypothesis that oxendolone in a dose of 200 mg i. m. once a week for 12 weeks is clinically useful in the conservative treatment of BPH.

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