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Norfenefrine in the Treatment of Female Stress Incontinence

A Double-Blind Controlled Trial

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Abstract. Forty-four consecutive patients with genuine stress incontinence were treated with norfenefrine 15–30 mg t.i.d. in a 6-week, double-blind and parallel, placebo-controlled study. Subjectively, 52% were improved and 26% became continent during norfenefrine treatment. Objectively (stress test), 30% became continent and the maximum urethral closure pressure increased 10% which was statistically significant. These results, however, were not statistically different from those of placebo treatment. Simultaneously, subjective and objective improvement was seen more often in patients given norfenefrine compared to placebo ($p < 0.1$). In patients with most severe incontinence according to urodynamic criteria the effect of norfenefrine was statistically significantly better than placebo. A low incidence of side effects was observed and no differences between norfenefrine and placebo were found. It is concluded that norfenefrine may be of value in the treatment of female stress incontinence.

Introduction

Stress urinary incontinence owing to urethral sphincter incompetence is preferably treated surgically. Conservative treatment, however, may be indicated when (a) the patient is waiting for surgery; (b) the degree of leakage is mild; (c) the patient is unwilling or unfit for surgery; (d) further childbearing is contemplated, and (e) the patient has increased risk of failure after surgery (obesity, chronic lung disease, low intra-urethral pressure, combined detrusor instability, etc.) [1]. The aim of pharmacological treatment of stress incontinence is to increase the urethral closure pressure by means of alpha-adrenergic agonists.

In a previous open study we found norfenefrine (Nevadral Retard®), an alpha-adrenergic agonist virtually free of beta-agonistic properties, to be effective in the treatment of stress incontinence without inducing significant side effects [2]. The aim of this study was to assess the subjective and objective efficacy of norfenefrine in patients with stress incontinence in a placebo-controlled trial.

Material and Methods

Based on data from the literature [3, 4], the placebo response rate was estimated as 15–20%, and the response rate during active treatment as 60–70%. The clinically meaningful difference was put to 40%, the error of the first kind to 5% and the error of the second kind to a maximum of 20%. Consequently, the sample size was calculated to a minimum of 40 patients.

Forty-seven females with genuine stress incontinence consecutively referred to the department during a 2-year period entered the study. Patients with severe genital prolapse, neurological disease, hypertension, heart disease, diabetes mellitus, organic bladder diseases, senility or in treatment with drugs acting on the lower urinary tract were not included in the study. Patients with detrusor instability or a residual urine (> 50 ml) on more than two readings were excluded. Informed consent should have been given by the patient prior to entering the study. The demographic details of the patients are shown in table I. All patients complained of hygienic and/or social problems due to involuntary loss of urine. Five patients had previously tried pharmacological treatment, 4 pelvic floor exercise without satisfactory effect, and 7 patients had previously undergone anti-incontinence surgery (table I).

Two patients discontinued the study, 1 due to headache and 1 for personal reasons. One patient was excluded retrospectively as the inclusion criteria were not fulfilled. Thus, the study population comprised 44 patients of whom 21 were allocated to receive placebo

(placebo group) and 23 to receive norfenefrine (norfenefrine group).

The urodynamic techniques and other diagnostic procedures have been described previously [2]. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted.

Patients were taking tablets containing either 15 mg of norfenefrine in a sustained release form or placebo tablets of the same appearance in a 6-week period. The daily dose was 1 tablet t.i.d. during the first 3 weeks. If the effect was unsatisfactory and the patient was free of side effects, the daily dose was then changed to 2 tablets t.i.d.

All patients were assessed after 3 weeks of treatment by an enquiry supplemented by pulse and blood pressure measurements. After 6 weeks of treatment the clinical and urodynamic evaluations were repeated. This study was approved by the regional scientific ethical committee.

Statistical Methods

The median or the frequency are used to describe data. The analysis is based on nonparametric tests (Fisher's exact, chi^2, Mann-Whitney's and Wilcoxon's paired rank-sum tests).

Probabilities ≤ 0.05 are considered significant. For estimations, the 95% confidence intervals (CI) are given.

Although we originally decided to use two-sided significance tests, we now consider the issue as one-sided; thus, the question is: Is Nevadral Retard better than placebo? The reason is that we have now followed approximately 100 patients treated with Nevadral Retard for several weeks and seen no case of aggravated stress incontinence. Accordingly, we use one-sided tests when a difference in efficacy between Nevadral Retard and placebo is analysed or estimated.

Results

Dose

In 78% of the patients in the norfenefrine group versus 81% in the placebo group the dose was increased after 3 weeks of treatment from 1 to 2 tablets t.i.d.

Effect on the Symptom Incontinence

Twelve patients (52%, CI 31–73%) in the norfenefrine group claimed reduced stress incontinence during treatment versus 7 (33%, CI 15–57%) in the placebo group. The difference of 19% is not statistically significant (CI −5% to +43%). Six patients (26%) in the norfenefrine group became subjectively continent, namely 5 patients in the reproductive age with grade II and 1 postmenopausal woman with grade II incontinence and without accompanying estrogen therapy. In the placebo group 3 patients (14%) became subjectively continent all 3 with grade II incontinence, 2 postmenopausal and 1 in the reproductive age. The difference of 12% is not significant (CI −8% to +31%). Among the postmenopausal females no tendency towards increased therapeutic effect was seen in patients with concomitant estrogen therapy.

A statistically significant reduction in the use of pants was found during norfenefrine treatment compared with placebo ($p < 0.05$). Five patients (5/12, 42%) became cured of urge incontinence during norfenefrine treatment versus 4 (4/7, 57%) in the placebo group.

Effect on the 'Sign' Stress Incontinence

Judged by the stress test, 7 patients in both groups became continent during treatment. Eleven patients (48%) were improved both subjectively and objectively (stress test) in the norfenefrine group versus 5 patients (24%) in the placebo group. The difference of 24% is close to statistical significance ($p = 0.09$; CI +1% to +47%). The apparent discrepancy that p is above 0.05 and CI does not include zero is explained by the fact that p is calculated exactly by permutations, while CI is calculated using a formula assuming approximation to an underlying normal distribution.

Effects on the Pressure Profile

The changes of the pressure profile during treatment are shown in table II. A statistically significant increase in maximum urethral closure pressure (MUCP) was found in both groups. Classifying the severity of incontinence urodynamically according to the lowest bladder pressure at leakage, as proposed by Kujansuu et al. [5], no significant effect of norfenefrine compared to placebo was found in the group of patients with mild stress incontinence ($P_{ves} > 100$ cm water at leakage, $n = 16$) whereas a significant effect was observed in the group of patients with moderate and severe stress incontinence ($P_{ves} \leq 100$ cm water, $n = 17$; $p < 0.02$). Only 33 cases were interpretable. Effect means subjective as well as objective (at the stress test) improvement.

Flow, Intravesical Pressure, Residual Urine Volume

Maximum flow rate, mean flow rate, intravesical pressure at rest and residual urine volume showed no significant changes during treatment with either norfenefrine or placebo.

Side Effects

In the norfenefrine group 1 patient discontinued the trial after 5 days because of headache. Two other patients reported headache of whom 1 had concomitant nausea. One complained of slight dizziness and palpitations and 1 patient reported increased appetite. In the placebo group 1 patient reported headache during treatment. Blood pressure and pulse rate showed no significant changes in either group during the study.

Table I. Demographic details of 44 patients with genuine stress incontinence

	Placebo group (n = 21)	Norfenefrine group (n = 23)
Median age, years (range)	45 (27–73)	47 (23–68)
Median weight, kg (range)	65 (50–100)	61 (50–85)
Median duration of symptoms, years (range)	7 (1–33)	5 (0.4–32)
Postmenopausal	8	7
Stress incontinence (n)		
Grade I	0	2
Grade II	20	19
Grade III	1	2
Accompanying (sensory) urge incontinence	7	12
Previous surgery (n)		
Anterior colporrhaphy	3	4[1]
Colposuspension	0	1[1]
Accompanying estrogen treatment (n)	5	7

The degree of urinary incontinence was classified according to Ingelman-Sundberg [21].

[1] One patient had both operations.

Discussion

Increasing the intra-urethral pressure by means of alpha-adrenoceptor agonists has been used therapeutically in the treatment of female stress incontinence [2–4, 6–15]. However, only few double-blind studies have been published to evaluate the clinical efficacy of these drugs (table III).

Table II. Urethral pressure profile parameters before and during treatment with placebo or norfenefrine: values are medians

	Norfenefrine			Placebo		
	pretrial	during treatment		pretrial	during treatment	
MUCP cm H_2O	50	55	$p < 0.01$	55	65	$p < 0.05$
FL, mm	31	31	n.s.	27	27	n.s.
Profile area, mm^2	163	182	n.s.	176	182	n.s.

n.s. = Nonsignificant; FL = functional urethral length.

Table III. Recent double-blind controlled studies of the effect of alpha-stimulation in female stress incontinence

Study (compound)	Effect parameters	Response rate		Active drug vs. placebo p value
		active drug	placebo	
Ek et al. [3], 1978 (PPA)	symptom improvement	55%	5%	< 0.05
	continence	9%	0	n.s
	stress test	31%	8%	n.s.
	MUCP (mean)	+4	−3	< 0.05
Ek et al. [4], 1980 (PPA)	symptom improvement	62%	0	< 0.05
	continence	23%	0	n.s.
	MUCP (mean)	+7	+1	< 0.05
Fossberg et al. [8], 1983 (PPA)	symptom improvement	60%	15%	< 0.05
	continence	0	0	n.s.
	MUCP (mean)	+13	+5	< 0.05
Gnad et al. [10], 1984 (midodrine)	symptom improvement	85%	55%	n.s.
	continence	62%	27%	< 0.05
	MUCP (mean)	+3	0	< 0.05
Lose et al. [present study], 1987 (norfenefrine)	symptom improvement	52%	33%	n.s.
	continence	26%	14%	n.s.
	stress test	30%	33%	n.s.
	MUCP (median)	+9	+8	n.s.

PPA = Phenylpropanolamine; n.s. = nonsignificant.

This study shows that norfenefrine provides an improvement of the symptom stress incontinence, the 'sign' stress incontinence and the MUCP. Although we did not obtain statistical significance when compared with placebo treatment, the subjective and objective effect of norfenefrine seems to be of a similar magnitude as that of other alpha-agonists [3, 4, 6–15]. Based on registration of the use of pants a statistically significant effect of norfenefrine compared to placebo was found. Furthermore, the subgroup analysis revealed a significant subjective and objective effect of norfenefrine in patients with severe incontinence based on objective criteria, namely bladder pressure at leakage.

Our data revealed no difference in response rate between postmenopausal patients with or without accompanying estrogen therapy. This is in accordance with the results published by Ek et al. [4]. Animal studies have shown that estrogens increase the number of alpha-adrenergic receptors in the urethra [16]. Whether changes similar to those seen in animals can be obtained in the human urethra remains to be established. Theoretically, the combination of an alpha-agonist and estrogens in postmenopausal patients might lead to an increased effect on the urethral closure function, as compared to the use of these drugs alone.

An unexpected finding in this study was a pronounced placebo effect on the symptom stress incontinence as well as the objective findings (stress test and MUCP). This high placebo reaction means that our pretrial estimation of the sample size was inadequate to prove a possible superior effect of norfenefrine. However, the data suggest that a larger double-blind study of norfenefrine may establish the efficacy of this agent. Therefore, the results of the present study might express an error of the second kind. Pronounced placebo response on symptoms as well as objective findings are well described when treating patients with urge incontinence where psychosomatic factors may be involved in the etiology [17]. Sparse information, however, seems to be available concerning placebo response when treating female stress incontinence where the etiology is most often ascribed to anatomic causes. Gnad et al. [10] reported that 27% of patients with stress incontinence became subjectively continent during treatment with placebo. Knejzlikova and Scracek [18] also reported a pronounced placebo response when treating patients with mixed stress/urge and pure stress incontinence. Our data confirm that a significant subjective placebo response may occur during pharmacological treatment of female stress incontinence. Furthermore, we observed objective improvement during placebo treatment, MUCP increased significantly and 33% of the patients obtained a negative stress test. This observed placebo response may be explained partly by 'regression towards the mean' a well-recognized phenomenon which means that patients are often admitted when spontaneous fluctuations give rise to aggravated symptoms which tend to be improved at later evaluation. Also, the attitude of the physician and the doctor-patient relationship may contribute to a pronounced placebo effect.

In this study no significant side effects, especially no blood pressure elevation, were observed, which is in accordance with previous reports [2, 19]. Using an alpha-adrenergic agonist blood pressure elevation, however, is a potential side effect. Thus, 50–85 mg daily of phenylpropanolamine has been reported to induce a hypertensive responses in young healthy adults [20]. In conclusion, we feel that the results of this and our previous study [2] suggest that norfenefrine often improves stress incontinence, and in view of the low incidence of side effects there may be an indication for its use.

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