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Symptomatic Treatment of Benign Prostatic Obstruction with Nicergoline: A Placebo Controlled Clinical Study and Urodynamic Evaluation

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Summary. A double-blind crossover study of the alpha-blocker Nicergoline was carried out in sixteen patients affected by benign prostatic bladder outflow obstruction. The "irritative" symptoms of prostatic hypertrophy, including nocturnal frequency and dysuria, were improved after Nicergoline significantly more than after placebo. In 10 further patients with prostatic hypertrophy, peak and mean flow rates increased by 50% and 77% respectively after the acute administration of Nicergoline. No side effects were detected. In conclusion Nicergoline seems to be active and well tolerated in the treatment of benign prostatic obstruction.

Key words: Benign prostatic obstruction, Nicergoline, Urodynamic evaluation.

Introduction

Benign Prostatic Hypertrophy (BPH) causing obstruction to urinary flow has been treated in the past mainly surgically; however, several authors have claimed that BPH can also be treated medically. Hormones [11], antiandrogens [10], dopaminergic agents [9] and spironolactone [8] have been investigated with varying results. The majority of these studies however showed no effect of these drugs in reducing the size of the enlarged prostate and up to now this goal cannot be achieved by medical treatment. However, symptomatic relief is possible in patients affected by BPH with the use of drugs with alpha adrenergic blocking activity.

The demonstration of alpha receptors in prostatic adenoma and its capsule as well as in the bladder neck, and the finding that increased alpha tone enhances urinary obstruction in BPH, have led to the use of these drugs in BPH [5–7]. Intravenous phentolamine and oral phenoxybenzamine have been used most commonly, with generally favourable clinical and urodynamic results but with frequent and sometimes severe side effects [3–6].

The goal of our study was to assess in patients affected by BPH the clinical usefulness of Nicergoline, an ergot derivative with powerful alpha-blocking activity [1, 2, 13] and good tolerance.

Patients and Methods

16 patients, 42 to 78 years of age (mean 60.5 ± 9.1 years), affected by BPH diagnosed on the basis of clinical history, rectal examination and intravenous pyelography, entered the study. The trial had a double-blind crossover design and the randomisation of active and placebo medication was by reference to tables of random sampling numbers. Patients on placebo medication were treated at the same time as those on active medication under identical environmental conditions. The patients were assessed at the end of a 3-day wash-out period for baseline values, after 3 days at the crossover point and after 3 further days at the end of the second treatment period. Some parameters were evaluated on a daily basis. No wash-out period was included at the crossover point.

The patients were allocated randomly to one of the two groups, one treated with Nicergoline (N) 4 mg vials, twice a day intramuscularly for 3 days and then for a further 3 days with identical placebo (P) vials in place of Nicergoline, given in the same way. In the other group the order of treatment was reversed so that patients were first treated with Placebo and then with Nicergoline.

The following parameters were checked during the study:

a) Subjective parameters, such as symptoms, scored 1 to 4 for increasing severity by an experienced urologist, including difficulty in starting micturition, impairment of urine flow and bladder tenesmus, were evaluated on the third day of each period.

b) Objective parameters, such as frequency of micturition by day and night and average urine volume per micturition, were checked daily.

c) At the end of each period of treatment, the urologist expressed his judgement on the efficacy of the treatment on a 5 point scale, ranging from definite improvement [1] to severe worsening [5]. At the same time, patients described their clinical condition by a visual analogue scale.

d) At the end of the study both the urologist and the patients, expressed a preference for one of the two periods of treatment (N or P). The two periods of treatment were evaluated statistically accord-

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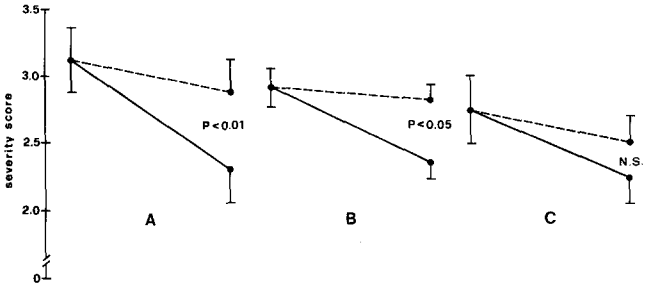

Fig. 1. Symptom severity score at basal conditions and after placebo (– – –) or Nicergoline (——) administration. *A* = Difficulty in starting micturition, *B* = Subjective impairment of urine flow, *C* = Bladder tenesmus

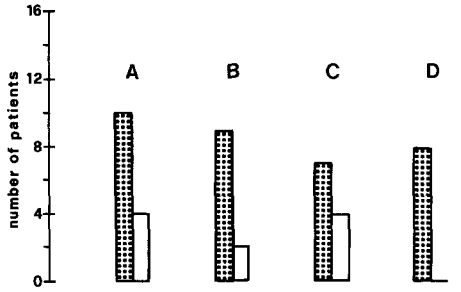

Fig. 2. Number of patients improved by 25% or more (compared to basal status) after Nicergoline (*hatched columns*) or placebo (*white columns*). *A* = Difficulty in starting micturition, *B* = Subjective impairement of urine flow, *C* = Bladder tenesmus, *D* = All symptoms together (sum of the three scores)

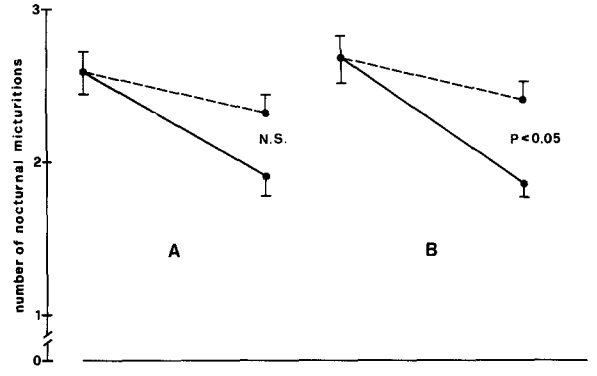

Fig. 3. Average number of nocturnal micturitions at basal conditions and during placebo (– – –) or Nicergoline (——) administration. *A* = 3 days of treatment, *B* = last 48 h of treatment

Table 1. Doctor's and patient's preference for Sermion (S) or placebo (P) treatment

	S better than P	S = P	P better than S	*n*	*P*
Doctor's Preference	12	4	0	16	<0.01
Patient's Preference	12	4	0	16	<0.01

ing to the non parametric method described by Koch [12], and the carry-over effect was evaluated according to the analysis of Wallenstein [15]. Independently from the placebo-controlled study, 10 additional consecutive patients, 56 to 76 years of age (mean age 67.4), affected by BPH, were tested by uroflow examination using a Wolf 2018.12 recorder, in basal conditions and 2 h after a single intramuscular injection of 4 mg of Nicergoline. The uroflow recodings in basal condition and after Nicergoline were compared using the Student's paired *t*-test.

Results

Clinical Study

All 16 patients completed the trial and no side effects were reported or observed.

The subjective parameters improved more after Nicergoline administration than after placebo: the difference of the severity score between treatments was statistically significant for the items "Difficulty in starting micturition" and "Subjective impairment of urine flow" (Fig. 1). Furthermore, the number of patients improved by 25% or more was higher after Nicergoline than after placebo (Fig. 2). The total number of micturitions and the average 24 h urine volume were not significantly affected by either treatment. The average number of nocturnal micturitions decreased more after Nicergoline than after placebo; the difference between the two treatments was significant when only the 2nd and 3rd days were considered (Fig. 3): in fact a carry-over effect of Nicergoline on the first day of placebo treatment was shown at the statistical analysis [15] for the sequence N→P.

The urologist judged the clinical condition as improved in 13 cases out of 16 and unchanged in three after Nicergoline; after placebo only three patients were judged as improved, the remaining 13 being considered as unchanged; this difference was highly significant ($P < 0.01$).

As far as patients' judgement was concerned, an improvement after Nicergoline was reported in 14 instances, and in six after placebo, the difference being significant ($P < 0.01$).

When the doctor and patients expressed their preference for one of the two periods of treatment, no one preferred the placebo period, while the majority preferred the Nicergoline period (Table 1).

Uroflow Study

The single values of peak and mean flow rates in basal conditions and after Nicergoline are shown in Table 2. Two hours after the single intramuscular injection of Nicergoline 4 mg, the mean percentage increase of the individual peak flow values was 50.1%: in one patient the increase was greater than 100%; in two it ranged between 51% and 100% and in seven between 20% and 50%. The absolute peak flow increase was 5 ml/sec (Mean ± SE: Basal status: 10.8 ± 1.7; after Nicergoline 15.9 ± 2.1). The mean percentage increase of the individual mean flow values was 77%: in three pa-

Table 2. Peak flow rate and mean flow rate in basal conditions and 120′ after Nicergoline 4 mg i.m. in 10 patients affected by BPH

	Peak flow rate		Mean flow rate	
	Basal [ml/s]	After Nicergoline [ml/s]	Basal [ml/s]	After Nicergoline [ml/s]
1)	13.0	21.0	6.6	10.3
2)	14.0	18.9	6.7	9.2
3)	8.0	20.2	2.6	8.6
4)	10.8	13.5	3.1	5.0
5)	6.5	11.0	2.1	4.6
6)	8.5	10.2	2.6	4.7
7)	15.8	22.1	7.7	9.4
8)	10.0	13.1	4.2	5.7
9)	13.2	15.9	5.7	7.4
10)	8.7	12.8	3.1	6.2
Mean:	10.9	15.9[a]	4.4	7.1[a]
± S.E.	1.7	2.1	1.4	1.5

[a] = $P < 0.01$ vs. basal values

tients the increase was greater than 100%, in three it ranged between 51% and 100% and in four between 20% and 50%. The absolute mean flow increase was 2.7 ml/s (Mean ± SE = Basal status 4.4 ± 1.4; after Nicergoline 7.1 ± 1.3).

Discussion

Our study was designed to evaluate the possibility of achieving symptomatic benefit in patients affected by BPH with the administration of the alpha-blocker Nicergoline, since the relief of symptoms is extremely important for patients waiting for surgery or for patients who cannot be treated surgically.

Since a symptomatic response to placebo is frequent in patients affected by BPH [4], a double blind cross-over design was chosen for this study.

Our results clearly show that Nicergoline is significantly more effective than placebo in relieving the symptomatology of BPH. The benefit achieved by patients after the administration of Nicergoline is particularly demonstrated by the preference for the drug expressed by 12 of them, while only four found no difference between the two periods of treatment, and none preferred the placebo period. If we look at the objective parameters, the improvement in nocturnal frequency was also more pronounced after Nicergoline than after placebo.

The improvement in the subjective symptoms could be due to an effect of Nicergoline on the hyperactive detrusor of patients affected by BPH; some investigators have in fact suggested that this hyperactivity could be secondary to an enhanced adrenergic tone, and therefore responsive to alpha-blockers [4].

As far as the uroflow examination is concerned, a good increase of the average peak and mean flow rates (especially the latter), was found.

This finding, which was expected because of the alpha-blocking property of the drug, is brought about by a reduction of the tone of the capsule and adenoma, which ultimately leads to a reduction of the obstruction.

However, it has to be noted that in this study, Nicergoline was administered as a single acute dose; it might then be possible that after prolonged period of treatment the improvement of urine flow could be greater.

In fact, the finding of a carry-over effect of Nicergoline, observed during the first day of the subsequent placebo treatment period, seems to demonstrate a lasting effect of the drug.

Although our 16 in-patients underwent prostatectomy at the end of the trial many patients affected by BPH are elderly and not suitable for surgery because of concomitant diseases. In such circumstances treatment with alpha-blockers is a useful alternative [4]. Intravenous phentolamine [5] and oral phenoxybenzamine [6] have been widely used for this purpose, with generally favourable clinical and urodynamic results; however the side effects have been frequent and sometimes severe [3–6]. In particular, in one study 46% of patients treated with phenoxybenzamine exhibited unpleasant side effects [8]. Reflex tachycardia and arterial hypotension, well known side effects of phentolamine and phenoxybenzamine, may be particularly harmful in these patients who are often elderly and affected by ischaemic heart disease [3–6]. On the contrary Nicergoline combines a good alpha-blocking activity and a fair tolerance, having been succesfully used even in patients with acute myocardial infarction without untoward reactions [14]. As a proof of this fact, no patient complained of side effects during the trial, making the use of Nicergoline particularly advisable in patients affected by BPH.

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