

NICERGOLINE IN THE TREATMENT OF NEUROPATHIC BLADDER DYSFUNCTION: A PRELIMINARY REPORT

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Summary. We have employed the alpha blocking drug Nicergoline in 14 patients with neuropathic bladder dysfunction of the upper motor neurone type.

The oral administration of 15-30 mg/day of this drug over a period of 9.5 months significantly improved the urodynamic parameters, with an increase of bladder capacity, a disappearance or amelioration of uninhibited bladder contractions and a decrease in urethral pressure, profile urethral length and residual urine.

Two patients with vesico-ureteral reflux present before treatment showed radiological improvement after Nicergoline administration.

Tolerance of Nicergoline had been excellent without appreciable side effects. In conclusion, Nicergoline seems to be active and well tolerated in the pharmacological treatment of neuropathic bladder dysfunction.

Key words: Paraplegia; Neuropathic bladder; Nicergoline; Alpha blocking agents.

Introduction

It is well known that the alpha-adrenergic blocking agents are effective in the treatment of the neurogenic bladder (Hachen, 1980; Mobley, 1976). They also produce a relaxing effect on the urethral smooth muscle (Donker *et al.*, 1972; Whitfield *et al.*, 1976), and also reduce the detrusor hyperactivity (Kaplan and Nanninga, 1979). Until now other drugs have been used, especially phenoxybenzamine hydrochloride, which is effective but is not commercially available in our country. It also has some undesirable side effects.

For the reasons mentioned above we have used in patients with a neuropathic bladder the ergoline derivative Nicergoline, which is widely used as vasodilator (Boismare *et al.*, 1981; Pony *et al.*, 1982), and is remarkably free of side-effects. Recently, Nicergoline has been used by Ronchi *et al.* (1982) in prostatic patients with encouraging results and good tolerance.

Material and Methods

Fourteen patients with a neuropathic bladder after spinal cord lesion were included in this study. The neurological deficit was complete in eight patients (six paraplegics and two tetraplegics), and incomplete in six. All patients had passed the stage of spinal shock at the time of the study, which was carried out between 6 months and 12 years after the accident, the average time being of 3.7 years.

The age of the patients ranged from 12-60 years, with a mean age of 37 years. All had unbalanced upper motor neurone bladders with high residual urine. None had been previously treated with alpha blockers. Eleven patients were completely incontinent (using a condom urinal) and

three patients were continent, although with some voiding disturbance.

Urodynamic and radiological investigations were performed in all the patients before beginning the treatment.

The urodynamic investigations were carried out using a multichannel apparatus which allows simultaneous recordings of bladder and rectal pressure and external sphincter electromyography. A urethral pressure profile was performed after these simultaneous recordings according to the Brown-Wickham method (Brown and Wickham, 1969).

The bladder pressure was measured with a 12 Foley catheter, using a slow filling rate of 20 ml/min and abdominal pressure was recorded by means of a flaccid balloon filled with 10 ml water. We have not used the electronic method of subtracting intrarectal pressure from intravesical pressure in order to obtain a better recording of uninhibited bladder contractions. The sphincter electromyography was performed using two wire electrodes inserted into the perineum in the vicinity of the prostatic apex. The neutral electrode was placed on the skin of the thigh.

The functional profile length was estimated according to the International Continence Society as the length of the urethra in which the urethral pressure exceeds bladder pressure (Bates *et al.*, 1977).

The radiological study included an I.V.P. and retrograde cystography.

After this initial evaluation the treatment with Nicergoline was started, being administered orally at a daily dosage of 15 mg in three divided doses. During the treatment the residual urine was checked daily and twice a day also the blood pressure. The appearance of the possible side effects of an alpha-adrenolytic therapy (nasal congestion, lethargy, dizziness, postural hypotension, etc.), was carefully observed.

After 15 days of treatment all the patients were urodynamically reassessed but radiological examinations were only carried out in cases with abnormalities at the initial evaluation.

The objective criteria of response were a decrease in residual urine (higher than a 10 per cent of bladder capacity), urodynamic improvement and radiological amelioration. In three patients with incomplete lesions and spontaneous voiding we also considered subjective criteria of improvement in the micturition pattern.

In the event of good response the treatment was continued with the same dosage. If the response was incomplete or poor the dosage was increased to 30 mg/day and a new evaluation was performed after 15 days of the 'high dosage regime'. If the higher dosage proved to be effective the administration of Nicergoline was continued at 30 mg/day. When there was lack of therapeutic response to this high dose regime of Nicergoline we tended to change to another alpha blocking agent or to consider a surgical intervention (transurethral sphincterotomy).

Statistical analysis were made using the Wilcoxon rank test for paired differences.

Results

All 14 patients completed the trial. The 15 mg/day dosage was sufficient in ten but in four it was necessary to increase the dose to 30 mg/day.

Tolerance has been excellent without side effects. Only one patient with an incomplete lesion complained of anejaculation, possibly due to

TABLE I
Urodynamic parameters before and after Nicergoline administration

	Bladder capacity (cc)	Maximum intravesical pressure (cm H ₂ O)	Residual urine (cc)	Urethral pressure (cm H ₂ O)	Profile length (cm)
Before	178 ± 93	63 ± 24	140 ± 61	107 ± 18	4.7 ± 1.4
After	239 ± 90	63 ± 26	26 ± 39	85 ± 26	2.3 ± 0.9
	p < 0.05	N.S.	p < 0.005	p < 0.005	p < 0.005

absence of emission, a known side effect of the alpha blocking drugs on the seminal tract (Hachen, 1980).

The duration of treatment ranged from 6–12 months, with an average time of 9.5 months. It was not considered necessary in any case to change to another alpha blocking agent or to perform an operation.

The urodynamic parameters before and after Nicergoline administration are shown in Table I and Figures 1 and 2.

The bladder capacity increased in nine patients and remained unchanged in five, the average increase being 34.26 per cent ($p < 0.05$).

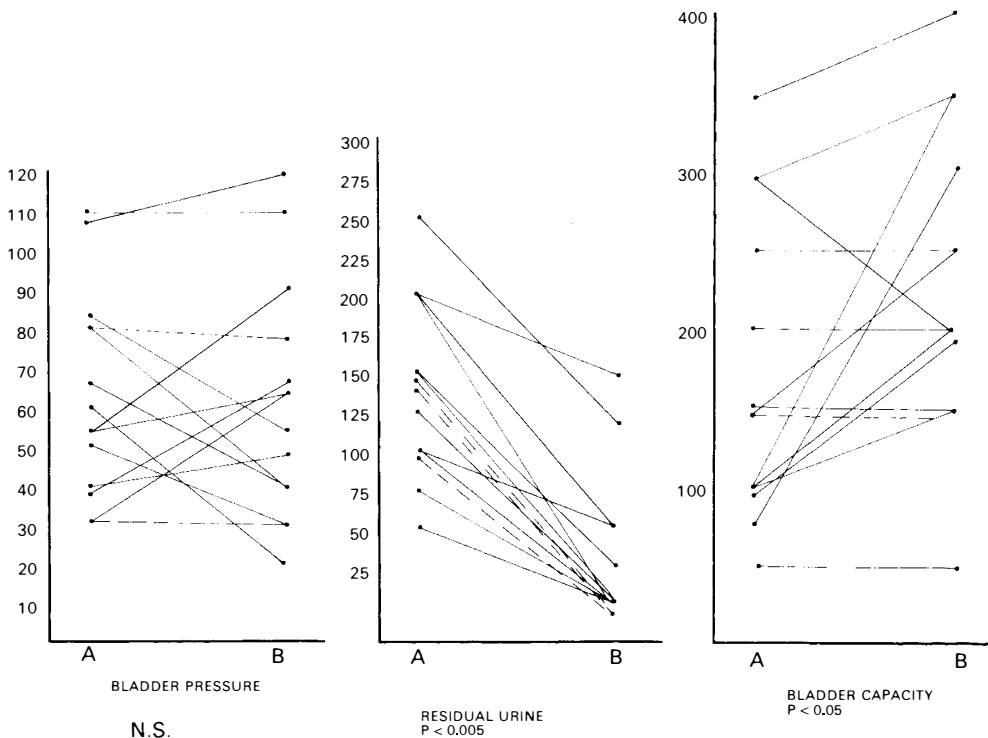


FIG. 1

Urodynamic parameters before (A) and after (B) Nicergoline administration. Bladder. Residual urine and bladder capacity: cc. Bladder pressure: cm H₂O. N.S.: no significant differences. The discontinuous line means equal values in different patient.

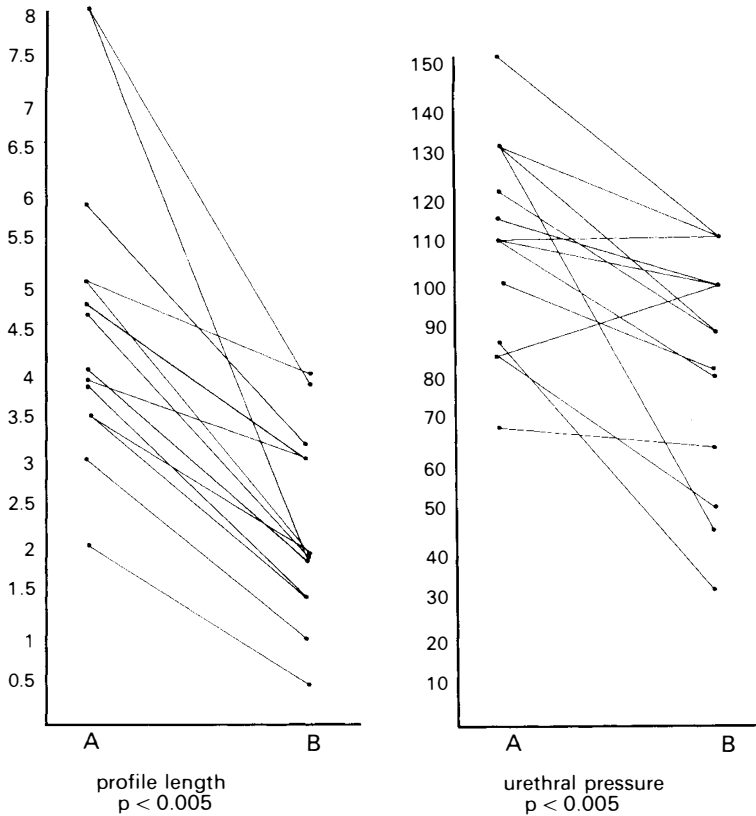


FIG. 2

Urodynamic parameters before and after Nicergoline. Urethra.

Residual urine decreased in all the patients, with an average decrease of 81.37 per cent in relation to the initial mean value ($p < 0.005$). In relation to bladder capacity the residual urine at the start of treatment was 78.65 per cent of bladder capacity, decreasing to 11.05 per cent of bladder capacity after Nicergoline administration.

The urethral pressure decreased in 13 patients. The reduction was 20.65 per cent of the initial mean value ($p < 0.005$) and the profile functional length decreased in all the patients, about 49.78 per cent of the initial mean values ($p < 0.005$).

No significant changes were found in maximal intravesical pressure. Detrusor waves were present in four patients, disappearing in three after Nicergoline administration. The vesico-sphincter dyssynergia (diagnosed through the simultaneous pressure/electromyography recordings in 11 patients), disappeared in six cases after treatment. The variable response of the striated sphincter is possibly due to the doubtful role of alpha receptors in this area (Rossier *et al.*, 1982).

The micturition pattern was tested in three patients with incomplete lesions and spontaneous voiding and all reported improvement in frequency and urgency.

Radiological alterations were found in two patients.

Case 1

A 28-year-old man was admitted with an incomplete spinal lesion below Th₅ due to a casual accident 4 years before.

He complained of frequency and urgency of micturition and had had recurrent episodes of acute pyelonephritis. The urodynamic study showed a bladder capacity of 100 cc, multiple detrusor waves and a residual urine of 50 cc. The urethral pressure was 110 cm H₂O and the profile length 5 cm.

The IVP showed right ureteropyelo-caliectasis (Fig. 3A) and the voiding cystogram right vesico-ureteral reflux grade IIb. After Nicergoline administration (15 mg/day) the voiding symptoms improved and the urodynamic investigation showed increased bladder capacity (200 cc), a decrease in urethral pressure (80 cm H₂O) and a decrease in profile length (3 cm). The IVP demonstrated marked improvement of the right ureteropyelo-caliectasis (Fig. 3B), although the vesico-ureteral reflux was still present in the voiding cysto-urethrogram. The persistence of the reflux is considered secondary to extra-vesicalisation of the intramural ureter as shown in Fig. 3B; however, we think that an antireflux operation is not necessary as the IVP remains improved and the pyelonephritic attacks have disappeared during the twelve months of treatment.

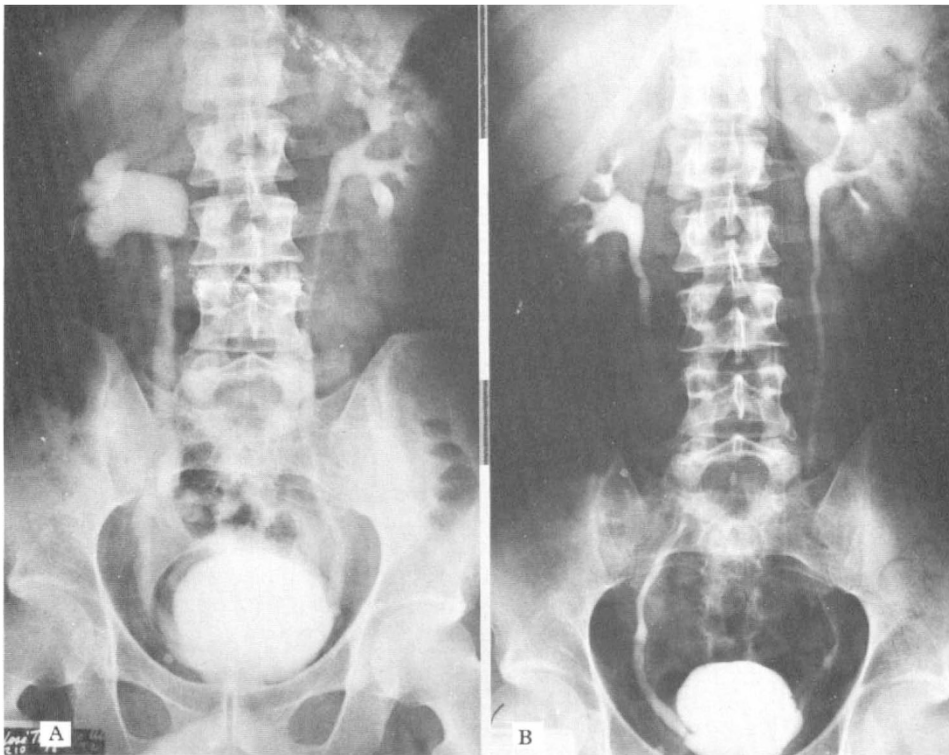


FIG. 3

Case number 1 I.V.P. at 10 minutes. (A) Before treatment. Right ureteropyelocaliectasis. (B) After treatment, showing marked improvement of right ureteropyelogram.

Case 2

A 50-year-old man, with an incomplete paraplegia below Th12, was admitted with a recent onset of episodes of fever, pyuria and left flank discomfort. Urine culture yielded more than 100,000 colonies per cc of *E. coli* but was sterilised by antibiotic therapy.

The urodynamic investigation showed a bladder capacity of 150 cc, a reflex bladder contraction of 54 cm H₂O of pressure and vesicosphincter dyssynergia. Urethral pressure was 110 cm H₂O, profile length 3.5 cm and residual urine 100 cc. The IVP was within normal limits but in the retrograde cystogram a left grade IIb vesico ureteral reflux, with a contracted bladder, was found (Fig. 4A).

Nicergoline was administered at a dose of 15 mgr/day without any significant improvement. When the dose was increased to 30 mgr/day, however, the urodynamic parameters improved, with disappearance of vesicosphincter dyssynergia. The residual urine was abolished, the urethral pressure fell to 84 cm H₂O and the profile length shortened to 1 cm. The retrograde cystogram demonstrated absence of reflux and disappearance of bladder wall trabeculation (Fig. 4B). The treatment continued for 12 months without recurrence of pyelonephritis.

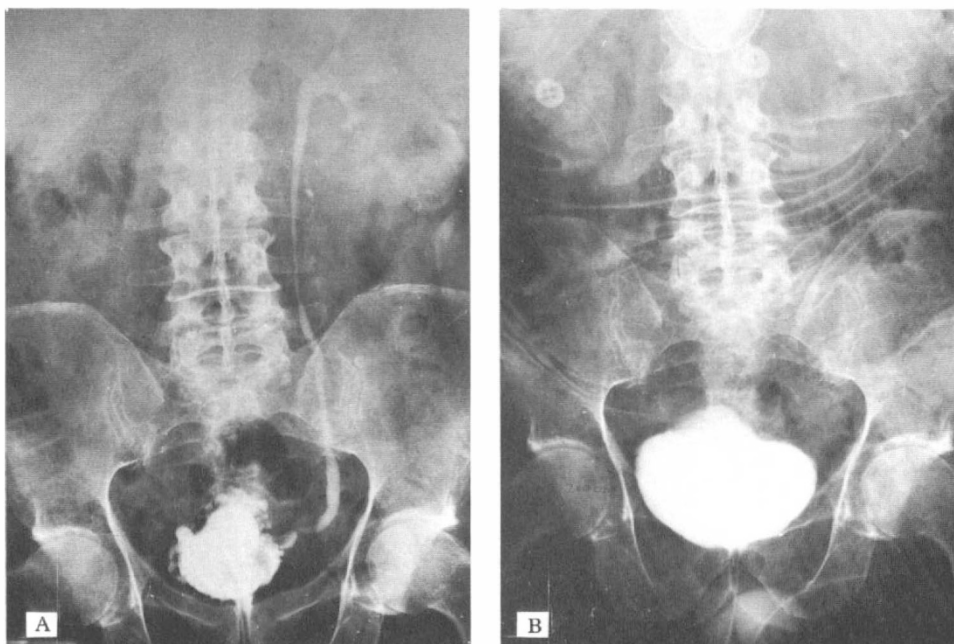


FIG. 4

Case number 2. Retrograde cystography. (A) Before treatment. Bladder wall trabeculation and left vesicoureteral reflux grade IIb. (B) After treatment. Vesicoureteral reflux has disappeared, and the bladder wall is smooth. Both films are made with 150 cc of contrast media.

Discussion

The presence of adrenergic receptors in the human lower urinary tract has been demonstrated both in the outflow region (Awad *et al.*, 1974) and in the prostate (Caine *et al.*, 1975). The pharmacological blockade with phentolamine of the alpha receptors causes a relaxation of the urethral smooth muscle fibres, with decrease in urethral pressure and urethral profile length (Donker *et al.*, 1972; Whitfield *et al.*, 1976). These effects are more evident in patients with a neuropathic bladder than in normal individuals (Rossier *et al.*, 1982), possibly due to an urethral hypersensitivity to alpha stimulation when bladder denervation is present. Koyanagi (1982) report an increase in blood catecholamines in patients with lower motor neurone lesions when placed in the sitting position, leading to an 'urethral sympathetic dyssynergia' that causes outflow obstruction in response to this postural discharge of catecholamines (Koyanagi *et al.*, 1982).

Nevertheless, Nordling, in histochemical studies of trigonal and bladder strips obtained from patients with neuropathic bladder, failed to demonstrate an increment in adrenergic fibres as an organic basis for urethral hypersensitivity (Nordling *et al.*, 1980).

From a clinical point of view the alpha blocking agents are being used increasingly in the management of the outflow urinary obstruction, both in neuropathic bladder (Hachen, 1980; Scott, 1978) and in prostatism (Caine *et al.*, 1976). The drug most commonly used is phenoxybenzamine hydrochloride, which causes urethral relaxation similar to phentolamine with the advantage of oral administration, thus allowing long term treatment. Furthermore, the bladder hyperreflexia improves with phenoxybenzamine by direct inhibition of the alpha receptors of the bladder and outflow region (Khanna, 1976), or by blocking the transmission in the parasympathetic ganglia surrounding the bladder (Rossier *et al.*, 1982). Scott *et al.* (1978) reported improvement in autonomic dysrreflexia with phenoxybenzamine but only if the drug is used previously to the stimulus (Scott *et al.*, 1978).

The dose of phenoxybenzamine varies between 10–30 mgr/day, seldom more (Mobley, 1976). Several authors (Hachen, 1980; Scott, 1978) report better results in lower motor neurone lesions, probably due to the urethral denervation hypersensitivity, while others (Mobley, 1976) report better results in reflex bladders.

Phenoxybenzamine has some side effects, including postural hypotension, nasal congestion, dizziness, tiredness and lethargy, which make it necessary to discontinue its administration in a 2.6 per cent–16 per cent of patients (Mobley, 1976; Scott, 1978). In order to obtain the same benefits of phenoxybenzamine without its side effects other alpha adrenergic blockers have been used.

Hence, Prazosin, a selective alpha 1 adrenergic blocking agent with less side effects, has a documented action on the urethra (Kiruluta *et al.*, 1981), and has been employed by Jensen with good results in four out of five patients with uninhibited bladder (Jensen, 1981).

Another drug investigated has been Thymoxamine (Pedersen *et al.*, 1980), which decreases urethral pressure and uninhibited bladder contractions thirty minutes after intravenous administration of 0.1 mgr/day. Nevertheless, Thymoxamine has not been used in a prolonged course of treatment.

Nicergoline is an ergoline derivative with alpha blocking activity (Arcari *et al.*, 1972) successfully used as vasodilating agent (Boismare *et al.*, 1981; Pony *et al.*, 1982), in vascular retinopathies (Bec *et al.*, 1976), and as an inhibitor of platelet aggregation (Migne *et al.*, 1974) with good tolerance in each case. Recently, Ronchi *et al.* (1982) have employed Nicergoline in patients with prostatism and report a good subjective and objective response (an increase in urinary flow), after a 3-day course or treatment with 4 mgr by intramuscular injection twice a day (Ronchi *et al.*, 1982).

The remarkable lack of side effects has encouraged us to use Nicergoline as an alpha adrenergic blocking agent in the management of neuropathic bladder, and, according to our experience, the first results are encouraging with regard to effectiveness and tolerance. It can be administered orally at a daily dose of 15-30 mgr.

We shall continue our study in order to obtain experience with more patients for longer periods and the long term results will be assessed.

Conclusions

1. Nicergoline, an alpha adrenergic blocking agent, is effective in the treatment of neuropathic bladder.
2. This drug is very well tolerated.
3. We consider that this drug deserves further investigation.

RÉSUMÉ

On a utilisé l'alpha-bloquant Nicergoline sur quatorze patients atteints de dysfonctionnement vésical neurogenique. On a employé une dose de 15-30 mg par jour, voie orale, pendant 9-5 mois.

On a constaté une amélioration urodynamique dans tous les patients, la diminution du résidu postmictionnel, l'augmentation de la capacité vésicale et la disparition ou diminution des contractions vésicales non inhibées. On a objectivé aussi la réduction de la pression urétrale de fermeture et de la longueur fonctionnelle due profil urétral.

Après l'administration de Nicergoline, on a eu une amélioration radiologique dans deux cas de reflux vésico urétéral.

La tolérance a été excellente, sans effets secondaires.

Enfin, nous croyons que la Nicergoline est un alpha-bloquant actif et bien toléré dans le traitement de la neurovessie.

ZUSAMMENFASSUNG

Wir haben das alfa blockierende Nicergoline bei 14 Patienten mit neurogenen Störungen der Blase eingesetzt. Die benutzte Dosis war 15-30 mgr. täglich, auf oralen Wege verabreicht, bei einer Durchschnittszeit von 9-5 Monaten.

Es konnte eine Besserung der Blasenfunktion in allen Fällen festgestellt werden, einhergehend mit einer Verminderung der Urinrückhaltung, Zunahme der Blasenkapazität und ein Verschwinden oder Zurückgehen der Blasenkontraktionen. Gleichzeitig konnte ein Abbau des Drucks des Harnröhrenverschlusses und ein Rückgang in der funktionellen Länge des Umrisses der Harnröhre festgestellt werden.

In zwei Fällen von Harnrückflüssen konnte radiologisch eine Besserung festgestellt werden, nach der Einnahme von Nicergoline.

Die Verträglichkeit war ausgezeichnet ohne Anzeichen von sekundären Störungen.

Zusammenfassend: Wir glauben, das Nicergoline als ein aktiver und gut verträglicher Alpha-Blocker bei der Behandlung der Blasenstörungen angebracht erscheint.

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