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The Effect of Nicergoline on the Lower Urinary Tract Muscle

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Summary. Two series of experiments were performed to determine whether nicergoline possesses an alpha-adrenergic blocking action on the lower urinary tract musculature in dogs and humans. One series consisted of in vivo studies of urethral pressure profile recordings in 19 female dogs, and their responses to adrenergic stimulation with noradrenaline or methoxamine, alone and following administration of nicergoline. The other series consisted of in vitro isometric studies of 61 strips of human prostate, and the establishment of dose response curves to nor-adrenaline alone and in the presence of various concentrations of nicergoline. In both sets of experiments clear evidence of an alpha-adrenergic blocking effect was obtained. From the in vitro experiments, the Kb of nicergoline was calculated as $\leqslant 9 \times 10^{-9}$ M.

Key words: Nicergoline, Alpha-adrenergic blockers, Prostate, Canine urethra.

Introduction

Nicergoline is a vasodilator which is used clinically for the treatment of cerebral and peripheral circulatory insufficiency, and which is believed to produce its effects by blockade of the alpha-adrenergic receptors in the smooth muscle of the blood vessels [1]. Alpha-blocking agents are of considerable value at the present time for the pharmacological treatment of a number of urological conditions because of their relaxant actions on the smooth muscle of the outflow tract from the bladder, but the number of such agents that are available for clinical use is very limited. It seemed therefore that it would be of interest and importance to determine if nicergoline exhibits an alpha-adrenergic blocking action on the smooth muscle of the lower urinary tract.

With this aim in view, two series of experiments were performed, one in vivo on the female canine urethra and the other in vitro on the human prostate. Each of these series of experiments, including the methods and results, will be presented in turn.

A. Canine Urethra

Material and Methods

Urethral pressure profile recordings were made on adult female mongrel dogs weighing from 10–24 kg, using the Brown and Wickham technique [4] with mechanical withdrawal of the catheter. A 3-hole catheter was employed, with infusion at the rate of 2.4 ml/min by a Harvard infusion pump, and the intraurethral pressures were recorded on a Hewlett-Packard 2-channel recorder. The dogs were anaesthetised with intravenous Sodium Pentobarbitone 30 mg/kg, together with gallamine 2 mg/kg to abolish striated muscle activity, with further additions of the drugs as necessary, and were mechanically ventilated via an endotracheal tube.

At least three initial recordings of the urethral pressure profile were obtained in order to establish a reproducible baseline. Following this an alpha-adrenergic agonist was administered intravenously, and its effect upon the alpha-receptors in the urethral muscle as indicated by a rise in the urethral closure pressure was recorded. In 13 instances nor-adrenaline was used for this purpose, and in 9 instances methoxamine was used. In the case of nor-adrenaline, on the basis of our previous experience, a dose of 5 micrograms/kg was used. In the case of methoxamine, three initial experiments were done with this substance alone, in order to establish a suitable dose and to determine the duration of its action. These indicated that a dose of 0.1 mg/kg was suitable, producing a good effect lasting approximately 40 min. In 7 of the 13 experiments using nor-adrenaline, propranolol 0.5 mg/kg was administered at the same time, in order to block any concomitant stimulation of the beta-adrenergic receptors also present in the urethra. In each experiment, after recording the urethral response to the adrenergic agonist, nicergoline was administered intravenously in a dose of 0.2, 0.3 or 0.4 mg/kg, following which the original agonist was re-administered and the new response of the urethra to the nor-adrenaline or the methoxamine was recorded. All urethral pressure profile recordings were repeated a number of times after the administration of each drug.

Table 1. Summary of results of in vivo experiments

	Noradrenaline + Nicergoline	Noradrenaline + Propranolol + Nicergoline	Methoxamine + Nicergoline
Blocking effect present	5	5	6
Blocking effect absent	1[a]	2	0
Total	6	7	6

[a] This experiment was technically unsuccessful, due to anaesthetic problems and haematuria with blood clots

Results (Table 1)

From the accompanying table it will be seen that in all 6 of the experiments using methoxamine, and in 10 out of the 13 experiments using nor-adrenaline, good evidence of a blocking effect of the nicergoline on the urethral alpha-adrenergic receptors was obtained (Fig. 1). In two of the remaining nor-adrenaline experiments no blocking effect was obtained, and in the third the experiment was technically unsuccessful due to anaesthetic problems and haematuria with blood clots. A diagram showing the results obtained in each of the individual dogs is given in Fig. 2.

In two instances, following the initial baseline recordings, the nicergoline was given prior to the first administration of the alpha-agonist, in both instances methoxamine. In each of these a reduction in the recording appeared following the nicergoline, and no response to the methoxamine was obtained. It was deduced that this was indeed due to

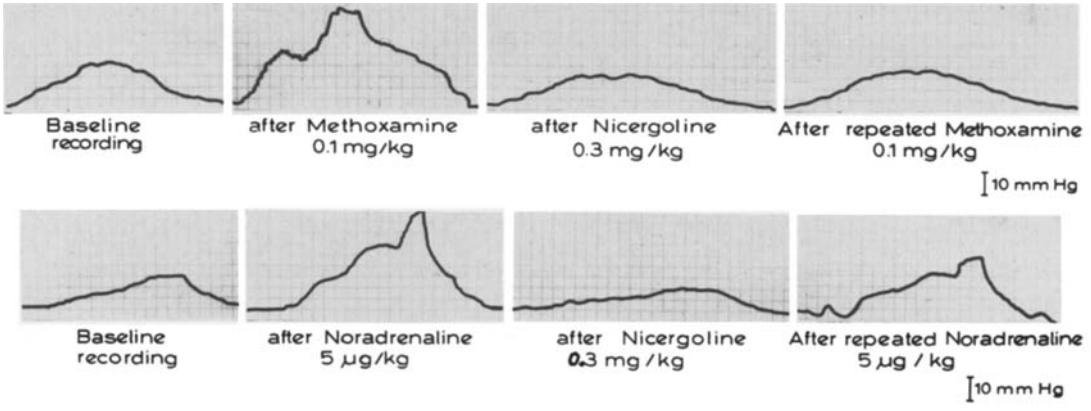
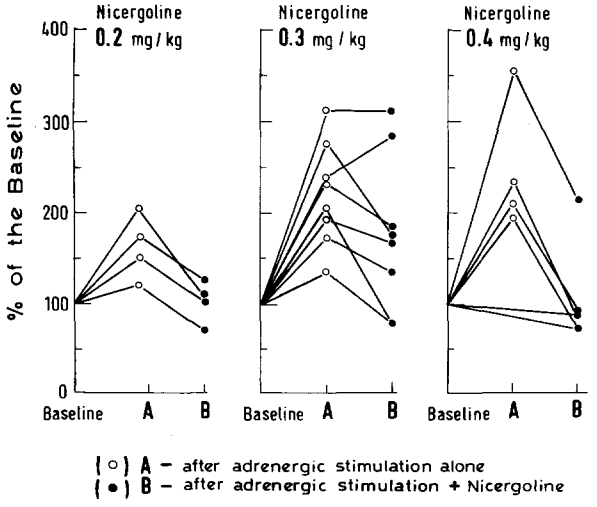


Fig. 1. Representative urethral pressure profile recordings in two dogs. In each case the following can be observed: The initial baseline recording, the rise in closure pressure due to adrenergic stimulation, the fall in the pressure recording following nicergoline, the reduced response to repeated adrenergic stimulation in the presence of the nicergoline

blocking of the alpha receptors and not just due to a failure of the dog to respond to the methoxamine, because in one of these cases a repeated injection of the methoxamine 80 min after the administration of the nicergoline, when its effect was beginning to wear off, did produce a response. In the other case, in addition to a similar late response to a second dose of the methoxamine, the same dog showed a definite reponse to methoxamine given initially on another occasion. These two experiments are therefore regarded as having given a positive response.



◀Fig. 2. The urethral pressure responses obtained in 18 dogs (1 experiment failed). In 16 cases the following three results are indicated: The maximal closure pressure in the initial baseline recording (= 100%), that following adrenergic stimulation alone, that following repeated adrenergic stimulation in the presence of the stated concentration of nicergoline. In the other 2 cases (in the 0.4 mg/kg group), the nicergoline was administered without prior adrenergic stimulation (see text)

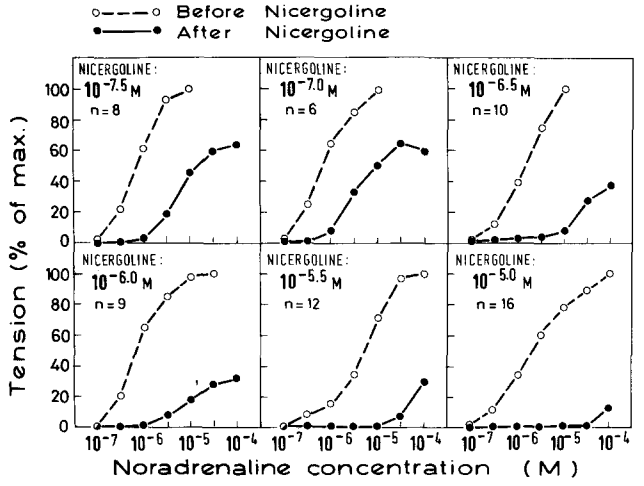


Fig. 3. Dose-response curves obtained in the human prostate, for noradrenaline alone and in the presence of increasing concentrations of nicergoline

B. Human Prostate

Material and Methods

Strips approximately 2 cm x 3 mm were prepared from human prostatic adenoma removed at open prostatectomy, and were examined by the in vitro isometric technique. Immediately after preparation they were placed in Krebs-Ringer solution at 5 °C, and subsequently examined in a muscle chamber containing the same solution with 5% glucose added, aerated with 95% Oxygen and 5% CO_2, at 37 °C. The tension in the strip was recorded on a Grass polygraph recorder via a Grass force-displacement transducer FTO3C. Following stabilisation of the preparation at a resting tension of 0.5 to 1 g, and the return of spontaneous activity, the dose-effect response to nor-adrenaline in concentrations of 10^{-7} M to 10^{-4} M was recorded. After washing the strip nicergoline was added, following which the response to the nor-adrenaline was re-examined. The concentrations of nicergoline used varied from $10^{-7.5}$ M to 10^{-5} M, and each strip of prostate acted as its own control. A total of 61 strips was examined by this method.

Results

Nor-adrenaline is known to stimulate the alpha-adrenergic receptors in the human prostate, resulting in a rise in tension in the strips [5]. In all the concentrations examined, nicergoline produced a definite blocking effect on these receptors, either reducing or completely abolishing the response obtained (Fig. 3). The degree of this blocking effect could best be determined from the four lower concentrations of nicergoline used as, owing to its potency, the two highest concentrations ($10^{-5.5}$ M and 10^{-5} M) were too powerful and flattened out the curve obtained almost completely. The Kb value, representing the dose of the blocker that halves the activity of the agonist, was evaluated for nicergoline from the resutls obtained in the four lower concentrations, and was found to be $\leqslant 9 \times 10^{-9}$ M, a figure which indicates a highly potent blocking action.

Discussion

Nicergoline is a semi-synthetic derivative of ergot alkaloids, which is well established as an alpha-adrenergic blocker of vascular muscle [1]. Unlike certain other ergot derivatives it does not have any direct stimulating effect on the smooth muscle, and does not act as a "partial agonist" [1]. Comparison of its efficiency in counteracting increased blood pressure produced by nor-adrenaline and adrenaline in the dog, has indicated that it is approximately three times as effective as phentolamine [7]. Recently, a double-blind crossover placebo-controlled clinical study of its use for the symptomatic relief of benign prostatic obstruction was published, and indicated a beneficial effect [9]. This study was based upon the premise that nicergoline would have a blocking effect on the alpha-adrenergic receptors in prostatic smooth muscle, but no laboratory investigations of such a possible action on the musculature of the lower urinary tract appear to have been published.

The results of both the present series of experiments appear to indicate quite clearly that nicergoline is an effective and potent blocker of the alpha-receptors which we have previously shown to be present in both the female canine urethra [8] and in the human prostate [5]. These findings support the theoretical rationale of the clinical trial referred to above.

If further studies confirm nicergoline to be clinically effective in the symptomatic treatment of benign prostatic hypertrophy, it may prove to have certain advantages over the other alpha blockers available at present. One of the disturbing side effects of most of these is their tendency to produce tachycardia. This seems to be a negligible feature with nicergoline, possibly because its blocking effect appears to be predominantly on the alpha-1, post-synaptic receptors [6]. The very minor degree of blocking action on the alpha-2, presynaptic adrenoreceptors means that the inhibitory feed-back mechanism controlling neuronal nor-adrenaline liberation will not be apprecibly interfered with, and this may explain this absence of tachycardia. Alternatively, this characteristic may be due to a central effect.

Another possible clinical advantage, as compared with other alpha-blocking agents, could relate to its cerebral action. There is evidence that nicergoline exerts a protective action against the effects of cerebral ischaemia. This appears, in the experimental animal, to be due to an action on the cellular metabolism or the stability of the cell membrane, rather than to be due simply to its vasodilator effect [2]. As one of the limiting factors in the use of other alpha-blockers is the fear of cerebral ischaemia, it could be that nicergoline would have a wider field of clinical use in patients with impairment of cerebral circulation.

It is noteworthy that the doses used in our in vivo experimental study were relatively high compared with the doses found effective in some of the cardio-vascular studies published, and in proportion to the doses used in patients. However, it may be that lower doses would also have an effect on the urethra. It is worth noting that whereas

Boismare et al. [3] reported that, in their experiments on the rat vas deferens, propranolol appeared to reinforce the alpha-blocking effect of nicergoline vis-a-vis nor-adrenaline, we did not see any evidance of this in the present series of experiments, in seven of which propranolol was used together with the nor-adrenaline.

In conclusion, the present investigation indicates that nicergoline has a potent blocking action on the alpha-adrenergic receptors in both the female canine urethra and the human prostate. This effect could be of clinical importance.

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