

The Effect of Methergin on the Lower Urinary Tract*

Shlomo Raz, Marcia Zeigler and Marco Caine

Department of Urology, Hadassah University Hospital,
and The Hebrew University-Hadassah Medical School,
Jerusalem, Israel.

Summary. The effect of Methergin on the lower urinary tract musculature was studied in female cats using an isometric muscle contraction technique. Methergin had a direct stimulatory effect on the bladder wall and no apparent effect on urethral muscle. Contrary

to current reports, Methergin showed alpha adrenergic blocking activity.

Key words: Methylergonovine, bladder, urethra, isometric, adrenergic receptors.

Introduction

As the urinary and genital tracts are closely related in their embryology and anatomy, hormonal sensitivities and functional activities, it seemed likely that they might also have similar pharmacological responses to certain drugs. Accordingly, the effects of ergot derivatives used to increase uterine contractions have been investigated clinically and experimentally on the urinary tract. The effects of ergot derivatives on smooth muscle are complex and some are even antagonistic due to the multiple activities of the drug (2, 6); because of their complex actions, ergot derivatives are used clinically only to obtain specific and well-defined effects. No clinical use of ergot derivatives is mentioned in the urological pharmacopoea.

For the past two years we have treated female patients suffering from lower urinary tract symptoms (frequency, urgency and dysuria) not related to urinary tract infection,

with an ergot derivative - Methylergonovine (Methergin, Sandoz), with encouraging clinical results. In order to elucidate the precise action of Methergin on the urinary tract a series of experiments has been performed in vitro using the technique of isometric muscle contraction.

Materials and Methods

Domestic cats weighing 2.5 - 3.0 kg. were anaesthetised intraperitoneally with 30 mg/kg sodium pentobarbital. Through a midline incision the bladder and urethra were removed taking special care to avoid stretching. The urethra was cut into transverse strips 0.5 to 1.5 cm in length, the bladder was cut into similar strips 0.5 to 1.5 cm in width, and the strips were immediately placed in Locke's solution No. 2 at 5°C. Each muscle strip was then examined by the isometric method in a 15cc muscle chamber containing Locke's solution No. 2 at 37°C, with 97% oxygen and 3% CO₂ bubbling through the solution. One end of the strip was fixed to the bottom of the chamber, and the other end was connected via a Grass Force Displacement Transducer FT.03C to a Low Level DC preamplifier and Grass Recorder. A sensitivity of 20 mm pen deflection per gram tension was used, and the recording speed of the paper was 10 mm

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per minute. The strips were submitted to a tension of one gram and spontaneous activity allowed to recover. The strips were tested by the addition of Methergin, Regitine, and noradrenaline to the muscle chamber. In all, fifty experiments were performed using this technique.

Results

It has previously been demonstrated under these experimental conditions that spontaneous contractions will appear in both bladder (5) and urethral muscles (8). In all the strips of urethra and bladder studied, spontaneous activity appeared, generally after about 30 min. The following results were then obtained:

A. Urethra

1. Regitine. Regitine 10 gamma/ml produced a marked diminution in the spontaneous activity and tone of the urethra in 9 out of 10 experiments (Fig. 1). The subsequent addition of Methergin did not influence the effect of Regitine.

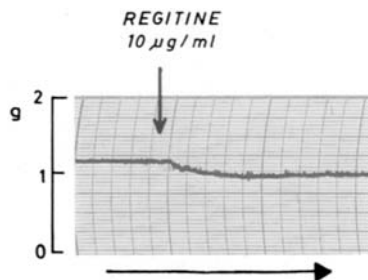


Fig. 1. Influence of Regitine on urethra. Regitine alone produced a fall in urethral tone.

2. Methergin. In 12 out of 20 experiments, Methergin 10 gamma/ml had no significant effect on spontaneous urethral activity; in 3 experiments there was a slight increase in the force and frequency of urethral contractions; in 5 there was a slight decrease in the basal tone and spontaneous activity of the urethra. The further addition of Regitine 10 gamma/ml produced either no change or a slight increase in urethral activity in 8 out of 10 experiments, and a fall in urethral activity in the remaining two experiments (Fig. 2).



Fig. 2. Influence of Methergin on Urethra. Methergin had no significant effect on the urethra. The subsequent addition of Regitine was then without effect, too.

3. Noradrenaline. The addition of noradrenaline 10 gamma/ml produced a marked rise in the tonus of the urethra in all 10 strips tested. The further addition of Methergin 10 gamma/ml blocked the noradrenaline effect (Fig. 3). The effect of noradrenaline, 10 gamma/ml, was completely inhibited by treatment with Methergin 10 gamma/ml (Fig. 4).

B. Bladder Wall

1. In 18 out of 20 experiments Methergin 10 gamma/ml produced a marked rise in basal tone and the force of contraction. The addition of Regitine 10 gamma/ml had no effect on the stimulatory action of Methergin (Fig. 5).

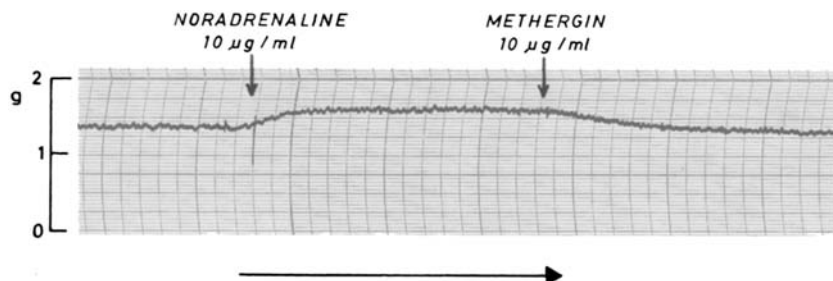


Fig. 3. Influence of Noradrenaline. Noradrenaline had an alpha adrenergic stimulatory effect on the tone of the urethra, which was blocked by Methergin.

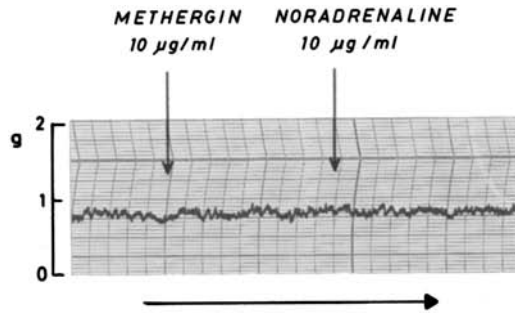


Fig. 4. Influence of Noradrenaline after Methergin. Noradrenaline given after Methergin had no effect on urethral tone.

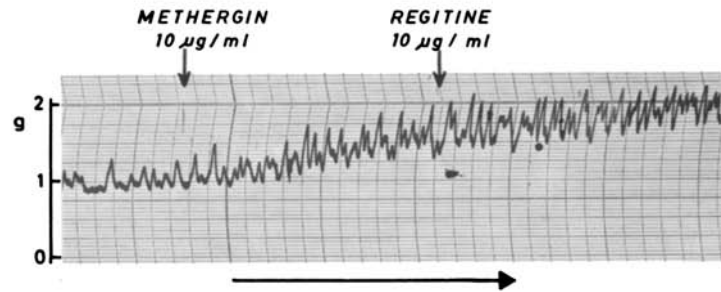


Fig. 5. Influence of Methergin on bladder wall. Administration of Methergin produced a steady rise in the tone of the bladder wall. Regitine did not block this stimulatory effect.

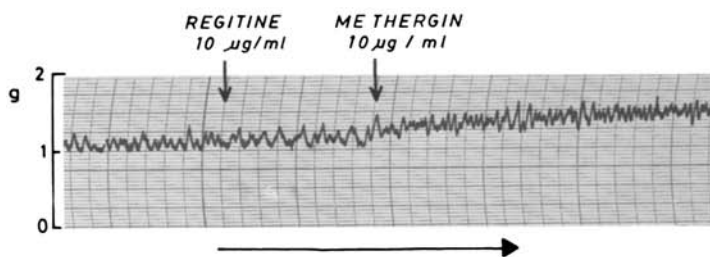


Fig. 6. Influence of Methergin after Regitine on bladder wall. Methergin given after Regitine caused stimulation of the bladder wall.

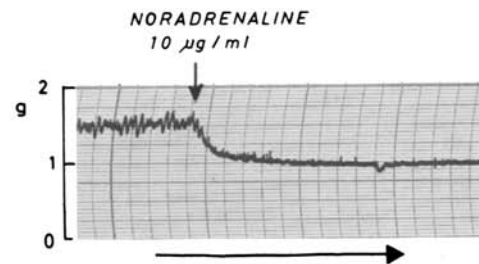


Fig. 7. Influence of Noradrenaline on bladder wall. Noradrenaline produced definite lowering of the tone and spontaneous activity of the bladder wall.

2. Regitine. Regitine 10 gamma/ml had no significant effect on the spontaneous activity of the bladder in 7 out of 10 experiments. In 3 experiments there was a slight decrease in the frequency of contractions. The further addition of Methergin 10 gamma/ml produced a rise in basal tone and frequency of contractions (Fig. 6).

3. Noradrenaline. Noradrenaline 10 gamma/ml in 10 experiments, caused a fall in basal tone and disappearance of spontaneous activity (Fig. 7). This action was not influenced by the subsequent addition of Methergin 10 gamma/ml.

Discussion

The net peripheral action of many ergot alkaloids is a combination of direct stimulation of smooth muscle together with a degree of adrenergic blockade. However, compounds of the ergonovine type, which lack a polypeptide side chain, are generally regarded as having no adrenergic blocking activity (4, 9, 11).

Previous studies have shown that the

urethra possesses both alpha and beta adrenergic receptors, with predominance of the former (7, 8). The alpha adrenergic effect is illustrated by the excitatory activity of noradrenaline. As clearly shown in Figs. 3 and 4, it was also possible to demonstrate an alpha adrenergic blocking effect of Methergin. The addition of Methergin blocked the alpha adrenergic action of Noradrenaline on the urethra, and pretreatment with Methergin inhibited this alpha effect. The experiments on the urethra with Regitine suggest the existence of a direct effect of Methergin on smooth muscle, too. Normally, Regitine has an inhibitory effect on the urethra (Fig. 1), but its addition to the urethra pre-treated with Methergin produced no significant change in urethral activity, suggesting that Regitine competes with Methergin as an alpha blocker, and that the alpha blockade is opposed and masked by the stimulatory effect of the Methergin. The observation that Methergin alone produced no significant change in urethral activity can be explained therefore, by the two mutually antagonistic actions of the drug (alpha blockade and direct stimulation) which tend to counterbalance one another.

It is very difficult to demonstrate the direct stimulatory action of Methergin as it is masked by its alpha blocking activity.

The bladder wall is rich in beta adrenergic receptors (5), as demonstrated by its inhibitory response to noradrenaline (Fig. 7). Methergin increased the tone and spontaneous rhythmic activity of the bladder wall (Fig. 5). Since the bladder has few alpha receptors, the alpha blocking effect of Methergin found in the urethra is of little significance, and the overall effect of the drug is of direct stimulation. That this represents a direct effect on the musculature and not alpha adrenergic stimulation is shown by the lack of any blocking effect by Regitine (Figs. 5 and 6).

In conclusion, contrary to what is generally reported Methergin has alpha adrenergic blocking activity, at any rate in the lower urinary tract. The response of the smooth muscle in a given organ depends on its content of alpha receptors. If a tissue is poor in alpha receptors, e.g. the bladder, the overall effect of Methergin will be stimulatory; whereas in tissues rich in alpha receptors, e.g. the urethra, the two opposing actions of Methergin will tend to cancel each other and the drug will have little or no ultimate effect.

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Shlomo Raz, M.D.
Department of Urology
Hadassah University Hospital
and The Hebrew University-Hadassah
Medical School
P.O.B. 499
Jerusalem 91000
Israel