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The Alpha-Adrenergic Blocking Effect of Prazosin on the Human Prostate

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Summary. The effect of prazosin on the adrenergic receptors in the human prostatic adenoma and prostatic capsule was investigated by an in vitro isometric technique. The results showed an alpha-adrenergic blocking action on both tissues. The cholinergic response of the capsule and the direct response of the adenoma were not affected. It is suggested that prazosin may prove preferable to phenoxybenzamine for clinical use as a prostatic alpha blocking agent, because of its selective action on the $alpha_1$ receptors.

Key words: Prazosin, Adrenoreceptors, Alpha-adrenergic blockers, Prostatic muscle

INTRODUCTION

In recent years Prazosin (1-(4-amino-6, 7-dimethoxy-2-quinazoline)-4-(2-furoyl)-piperazine) (Minipress) has come to be accepted as a potent anti-hypertensive agent. Originally its actions were thought to be due to a direct relaxing effect on the smooth muscle of blood vessels, but subsequently it became evident that the drug has a blocking action on the post-synaptic ($alpha_1$) alpha-adrenergic receptors (4, 5).

Our previous studies have demonstrated the presence of a high alpha-adrenergic receptor content in the enlarged human prostate, both in the adenomatous portion of the gland and in the surgical capsule (1). The purpose of the present study was to ascertain whether prazosin has a demonstrable alpha-adrenergic blocking effect on human prostatic muscle.

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MATERIAL AND METHODS

Strips approximately 2 mm wide by 2 cm long were removed at the time of retropubic prostatectomy from the anterior prostatic capsule and from the enucleated adenoma, as described previously (1). These were immediately placed in Krebs-Ringer solution at 5°C, and subsequently transferred to a muscle chamber containing the same solution with 5% glucose at 37°C, aerated with 95% oxygen and 5% CO_2, where they were examined by an isometric technique. The tension in the strip of tissue was recorded via a Grass force displacement transducer (FT O3C) onto a Grass polygraph recorder, calibrated to a sensitivity of 20 mm deflection per gram tension in the case of the capsule, and 20 mm per 0.5 gram tension in the case of the prostate. The strips were subjected to between 0.5 and 1.0 gram resting tension and, following a period of stabilisation and the recovery of spontaneous activity, the isometric reactions to adrenergic stimulation and the effect on these of the addition of prazosin were studied. Pure prazosin HCl was supplied by the manufacturers, Pfizer International Inc., for the purpose of these experiments. It is soluble in water (1.4 mg/ml), and was used in aqueous solution at final concentrations of 1 γ and 2 γ/ml. In the majority of cases nor-adrenaline was used as the adrenergic agonist in a concentration of 10 γ/ml. Following addition of prazosin, the concentration of nor-adrenaline was greatly increased to try and elicit a response. In 5 instances metaraminol (Aramine) was used as an agonist, either alone or in addition to the nor-adrenaline.

RESULTS

Altogether, 51 experiments were performed, 24 on the prostatic capsule, and 27 on the prostatic adenoma. Two specimens from the adenomas

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failed to show signs of activity, but all the other specimens gave a uniform type of result, which varied in degree from specimen to specimen.

As was to be expected, addition of the adrenergic agonist produced an increase in tension in the strips, due to stimulation of the alpha-adrenergic receptors that we have previously demonstrated to be present in both the prostatic adenoma and the prostatic capsule. Subsequent addition of the prazosin abolished this effect in all instances, with return of the tension to the baseline or occasionally below it (Figs. 1 and 2). Subsequent

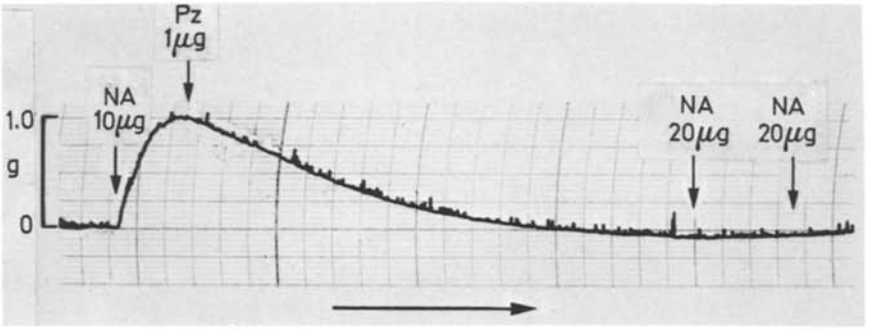

Fig. 1. Alpha-adrenergic stimulant effect of nor-adrenaline on prostatic capsule, blocked by subsequent addition of prazosin. Further addition of high concentrations of nor-adrenaline failed to elicit response

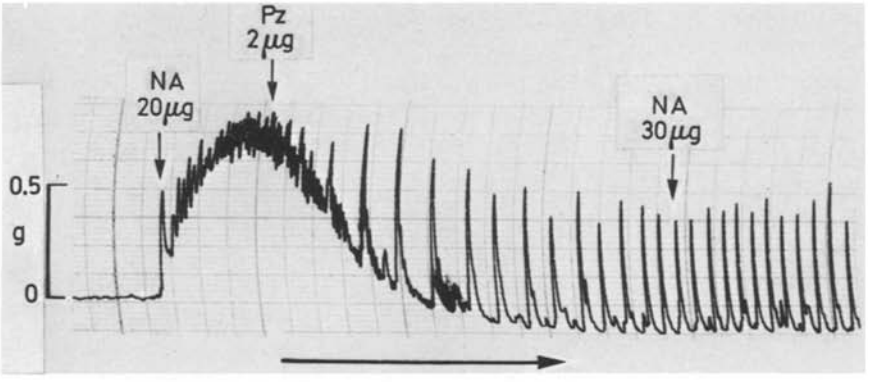

Fig. 2. Alpha-adrenergic stimulant effect of nor-adrenaline on prostatic adenoma, blocked by subsequent addition of prazosin. No response to further addition of nor-adrenaline

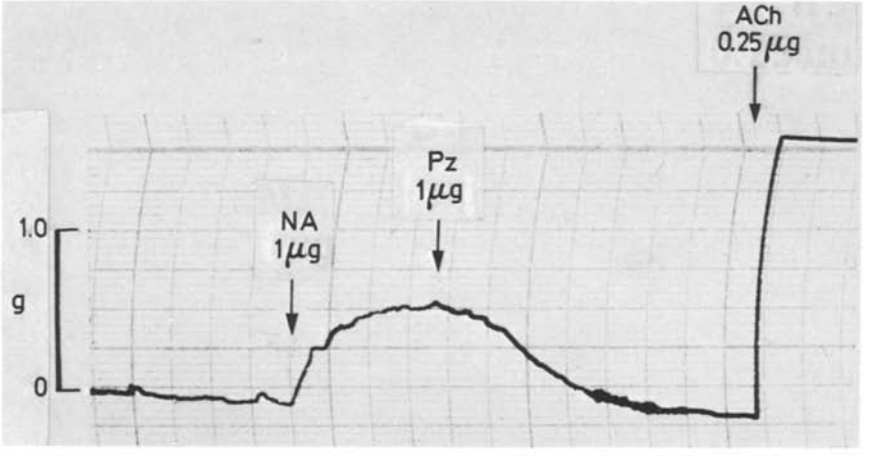

Fig. 3. Response of prostatic capsule to nor-adrenaline abolished by prazosin, but response to subsequent addition of acetylcholine retained

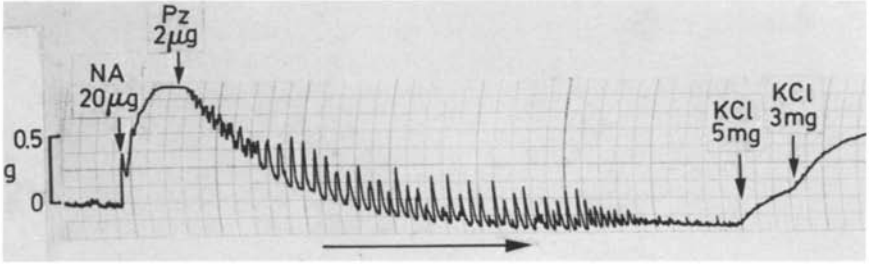

Fig. 4. Response of prostatic adenoma to nor-adrenaline abolished by prazosin, but response to subsequent addition of potassium chloride retained

further addition of the agonist usually failed to produce any further response, although in a few cases the addition of very high concentrations of nor-adrenaline did produce a very slight increase in tension once again. When the prazosin was added first (14 instances) it prevented the alpha-adrenergic response to the agonist. The fact that the abolition or prevention of the alpha-adrenergic response following prazosin was due to an alpha-adrenergic blockade and not due to a non-specific effect on the muscle fibres, was shown by the fact that a marked increase in tension could still be elicited by the subsequent addition of acetylcholine to the capsular specimens (Fig. 3), and by the addition of potassium chloride to the adenomatous specimens (in which cholinergic receptors are lacking) (Fig. 4). It is noteworthy that it was found virtually impossible to wash out the prazosin from the muscle strips.

DISCUSSION

A large amount of scientific and clinical work has been published during the last few years on the pharmacological actions of prazosin, but references to a possible effect on the lower urinary tract musculature are scanty. A clinical indication of an effect on the female human urethra was furnished by Thien et al. (8), who reported that three out of 30 patients treated by them developed incontinence. In one case described in detail, a mild stress incontinence was converted to complete incontinence following 4 weeks treatment of hypertension with prazosin, but recovered immediately after withdrawal of the drug. Urethral pressure profile measurements in this patient showed a drop in the closure pressure following treatment, and there was an increase in maximal urinary flow rate from 38 ml/sec to 47 ml/sec.

It is interesting that Koshy et al. (6) state specifically that none of their nine male patients treated with prazosin had failure of ejaculation, as an effective alpha-adrenergic blocking agent acting on the bladder neck would be expected to result in retrograde ejaculation in a proportion of cases. However, a review of 200 of our patients treated with phenoxybenzamine, an alpha-blocker which has been clearly shown to relax the muscle of the prostate and bladder neck, showed that retrograde or delayed ejaculation occurred in only 4.5%, so that the absence of this effect in only 9 patients treated with prazosin is not necessarily of significance. A recent report by MacGregor and Diokno on an in vivo study of the action of prazosin on the dog urethra (7) showed a fall in the maximal intra-urethral pressure, which could not be reversed by ephedrine.

Our present studies are, to the best of our knowledge, the first to examine directly the action of prazosin on the human prostatic musculature. Our findings, that it abolishes the alpha-adrenergic response to sympathetic agonists, or that by prior administration it prevents such a response, together with the demonstration that the muscle still retains its ability to contract forcefully to a different type of stimulus, clearly indicate that prazosin is effective in blocking the alpha-adrenergic receptors in the smooth muscle of both the prostatic adenoma and prostatic capsule.

We have on a number of occasions demonstrated the beneficial effects of blockade of the alpha-adrenergic receptors in the human prostate in cases of benign prostatic obstruction (2, 3), and in view of our findings in the present investigation it is reasonable to assume that prazosin will have a similar action. Theoretically, there could be an advantage in using prazosin rather than phenoxybenzamine, the drug normally employed up till now. Phenoxybenzamine is believed to block both the post-synaptic receptors ($alpha_1$) and the pre-synaptic receptors ($alpha_2$). The latter effect will reduce the negative feed-back mechanism normally controlling the release of nor-adrenaline at nerve terminals, and thus a larger amount than normal will be liberated, which may to some extent counteract the blockade produced on the post-synaptic receptors, as well as producing unwanted systemic effects. If the blockade is limited to the post-synaptic receptors, as is believed to be the case with prazosin, the negative feed-back mechanism should be unimpaired, thus resulting in a more effective blockade. It is intended to investigate the clinical implications of our findings.

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