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Pilot experiments on the actions of drugs injected into the human corpus cavernosum penis

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1 Seven drugs that are known to relax smooth muscle (phenoxybenzamine, phentolamine, thymoxamine, imipramine, verapamil, papaverine, naftidrofuryl) caused erection when injected intracavernosally.

2 Salbutamol, hydralazine, lignocaine and bupivacaine caused tumidity but not erection.

3 Metaraminol and guanethidine caused shrinkage followed by tumidity.

4 Neostigmine, atropine, propranolol and idazoxan had no effect in the doses tried.

5 It is argued that the seven drugs that cause erection do so by relaxing vascular and trabecular smooth muscle within the cavernosal space, and that the two that cause shrinkage of the penis do so by constricting vascular and trabecular smooth muscle within the cavernosal space.

6 It is argued that muscarinic and β-adrenergic transmission play no important part in erectile mechanisms within the corpora cavernosa.

7 Papaverine, phenoxybenzamine and metaraminol, given intracavernosally, are already used therapeutically. Uses are suggested for thymoxamine, phentolamine, verapamil and guanethidine.

Introduction

Papaverine (Virag, 1982) and phenoxybenzamine and phentolamine (Brindley, 1983a; 1983b) cause erection when given by intracavernosal injection. Metaraminol, given by the same route, shrinks the penis (Brindley, 1984a). These drugs are now in therapeutic use (Virag, 1982; Virag *et al.*, 1984; Brindley, 1983b; 1984a,b; 1986; Zorgniotti & Lefleur, 1985). In the course of developing treatments for erectile impotence and priapism that use them, I made, on myself as subject, observations on the actions of a number of other drugs given by the same route. This paper reports these observations and makes some physiological inferences.

Methods

Drugs were injected through a 0.5 mm × 16 mm needle into the right corpus cavernosum in the proximal third of the free penis. The penis was then massaged systematically to distribute the drug throughout both corpora cavernosa as follows. First, the right corpus cavernosum was squeezed between the thumb and three fingers of the left hand distally and the thumb and three fingers of the right hand proximally, both hands acting simultaneously; then the left corpus cavernosum was squeezed in the same way; then the penis was firmly pinched transversely at least six different places along it length in succession. These three actions were then repeated.

The drugs were injected in a volume of 2 ml or less, except for phenoxybenzamine, hydralazine and naftidrofuryl, which were diluted with 10 ml of 0.9% sodium chloride solution. The passive swelling caused by injection of 10 ml of solution is so slight as to be difficult to see.

The length of the penis was measured with the simple special instrument shown in Figure 1. The cylinder was pressed against the symphysis pubis. The penis was then laid on the V-section gutter, and the position of its tip read against the scale marked on the gutter.

The stiffness of the penis was assessed by attempting to bend it to right and to left with the fingers, applying forces of about 500 g wt in opposite directions to the glans and the middle of the shaft. In Tables 1 and 2, 'flexible 20°' means that this procedure caused it to bend through an angle 20°, i.e. so that the central axes of the proximal and distal ends intersected at an angle of 160°.

Drugs were obtained from the following sources. Phenoxybenzamine hydrochloride, Smith Kline &

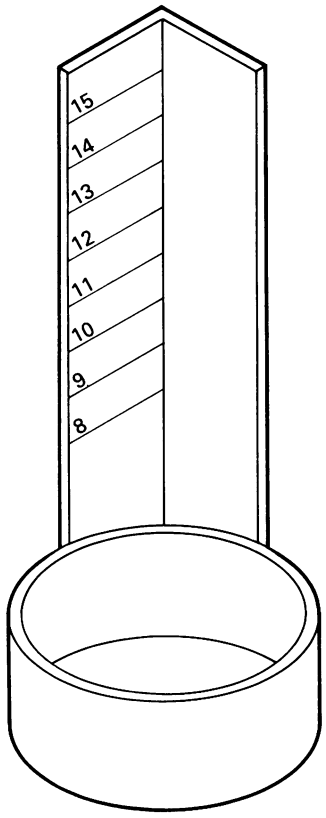

Figure 1 Simple instrument for measuring the length of the penis. The cylinder is of internal diameter 6 cm and length 5 cm. The angle between the planes of the V-section gutter is 90°.

French; phentolamine mesylate, Ciba; thymoxamine hydrochloride, Parke Davis; imipramine hydrochloride, Geigy; verapamil hydrochloride, Abbott; papaverine sulphate, Macarthys; naftidrofuryl oxalate, Lipha; salbutamol sulphate, Allen & Hanburys; hydralazine hydrochloride, Ciba; lignocaine hydrochloride, Astra; bupivacaine hydrochloride, Astra; metaraminol tartrate, Merck, Sharp & Dohme; guanethidine monosulphate, Ciba; neostigmine methylsulphate, Roche; atropine sulphate, Antigen; propranolol hydrochloride, ICI; idazoxan; Reckitt & Colman.

Results

Drugs that consistently cause erection

These are shown in Table 1. When the penis was long (> 12 cm), the cavernosal space was always tumid, except during the first half minute, when all these drugs caused conspicuous elongation before tumidity was visible or palpable.

Injection of an appropriate dose of phenoxybenzamine or papaverine is followed by an unrelenting erection lasting for hours. The duration is clearly dose-dependent for papaverine. For phenoxybenzamine the duration for a constant dose of 4 mg is rather variable, and no higher dose was tried, because of the priapism that occurred once after 4 mg.

Imipramine had two other effects besides the tumidity and erection shown in Table 1. Firstly, from about the fifth to the fortieth minute there was partial anaesthesia of one or both corpora cavernosa. For one of the 12.5 mg doses this was clearly present on both sides; for the 5 mg dose and the other 12.5 mg dose it was detectable only on the side of injection. Secondly, from about the twentieth to the hundredth minute after both 12.5 mg doses the glans was strikingly paler than usual, and from about the fortieth to the hundredth minute the penis was smaller than would have been expected for my thermal state. The delayed effect of imipramine 12.5 mg on the glans was as striking as the similar early effect of guanethidine 10 mg. The delayed effect of imipramine 12.5 mg on penile size was not as great as the similar early effect of guanethidine 10 mg (see below). The 5 mg dose of imipramine had no detectable late effect on colour of the glans or on size of the penis.

Drugs that cause tumidity of the corpora cavernosa but do not consistently cause erection

These are shown in Table 2. Blood pressure measurements show that the somewhat surprising failure of hydralazine to cause erection is not due to hypotension.

The 5 mg dose of lignocaine caused incomplete anaesthesia of the deep tissues of the shaft of the penis. For all larger doses of lignocaine, and both doses of bupivacaine, anaesthesia of deep tissues seemed to be complete (including the corpus spongiosum and deep tissues of the glans), but the skin, including that of the glans, was unaffected. Complete anaesthesia lasted about 30 min after lignocaine injections and about 40 min after bupivacaine.

The experiments of 10.4.85, were done blind, one at 10 h 00 min (bupivacaine), and the other 15 h 00 min (lignocaine).

Drugs that cause shrinkage of the penis, followed by tumidity

These are shown in Table 3. After metaraminol the shrinkage was conspicuous, and the subsequent enlargement not great. Both were dose-dependent. After guanethidine the shrinkage was dose-dependent, and

Table 1 Drugs that cause erection

Drug and dose (mg)	*Date*	*First not flexible 90°*	*First not flexible 20°*	*Not flexible 20° until*	*Not flexible 90° until*	*12 cm long until*
Phenoxybenzamine 2	27. 9.83	8 min	—	—	5 h	22 h
Phenoxybenzamine 2	22.11.84	3 min	—	—	4.5 h	25 h
Phenoxybenzamine 4	18. 4.83	8 min	17 min	5.25 h	5.25 h	31 h
Phenoxybenzamine 4	15. 8.83	5 min	6 min	15 h*	15.25 h*	33 h
Phenoxybenzamine 4	10.11.83	3 min	5 min	6.5 h	7.5 h	44 h
Phenoxybenzamine 4	19. 4.84	6 min	24 min	2.25 h	2.75 h	26 h
Phenoxybenzamine 4	19. 2.85	16 min	30 min	2.75 h	4 h	36 h
Phentolamine 1	5.12.84	1 min	—	—	2.5 min	23 min
Phentolamine 3	17. 9.83	1.5 min	2 min	4.5 min	11 min	90 min
Phentolamine 5	31. 5.83	1.25 min	1.75 min	4 min	12.5 min	85 min
Phentolamine 10	6.11.84	0.75 min	1.5 min	3 min	14 min	82 min
Thymoxamine 1	4.11.84	—	—	—	—	18 min
Thymoxamine 2.5	8. 1.85	1 min	—	—	3 min	22 min
Thymoxamine 7	18.10.84	1 min	1.5 min	3 min	6.5 min	34 min
Thymoxamine 10	6.11.84	0.75 min	1.5 min	3 min	14 min	32 min
Papaverine 5	10.11.84	1.5 min	2 min	3 min	7 min	40 min
Papaverine 10	15.11.84	0.75 min	1 min	2 min	42 min	63 min
Papaverine 20	10. 1.85	0.75 min	1.5 min	45 min	98 min	130 min
Papaverine 40	2.12.83	1 min	1.5 min	64 min	126 min	150 min
Papaverine 40	4. 4.84	1 min	1.5 min	130 min	3.5 min	4.5 h
Papaverine 80	30.11.83	1 min	2 min	5 h	5.5 h	6.5 h
Papaverine 120	20. 6.85	0.75 min	1 min	4.5 h	5.5 h	6 h
Verapamil 0.5	3.12.84	min	3 min	4 min	5.5 min	16 min
Verapamil 0.5	22. 6.85	1.25 min	—	—	5.5 min	27 min
Verapamil 1	3. 9.84	2 min	3 min	5 min	8 min	52 min
Verapamil 3	4. 9.84	1 min	2.5 min	4 min	8 min	60 min
Verapamil 5	1.12.84	0.75 in	1 min	4 min	14 min	65 min
Naftidrofuryl 10	6.11.84	—	—	—	—	11 min
Naftidrofuryl 20	23. 9.83	3 min	5 min	5.5 min	9 min	25 min
Naftidrofuryl 25	17.10.84	3 min	4 min	5.5 min	14 min	30 min
Imipramine 5	4. 5.85	1.5 min	2 min	5 min	11 min	32 min
Imipramine 12.5	18.11.83	2.5 min	4 min	7 min	19 min	31 min
Imipramine 12.5	6. 9.84	2 min	3.5 min	7 min	13 min	25 min

*Priapism successfully treated with metaraminol.

slight except with the largest dose. The subsequent enlargement was conspicuous. With both drugs the glans was strikingly pale during the first half to one hour.

Drugs that had no detectable effect in the doses tried

The following caused no visible swelling or measurable elongation of the penis, and did not prevent the achieving of full erection by sexual fantasy (sometimes supplemented by applying a vibrator to the glans) at between 10 and 20 min after giving the drug: neostigmine 0.25, 0.3 and 0.5 mg; atropine 0.3 and 0.6 mg; propranolol 0.3 and 0.6 mg; idazoxan 0.05, 0.2, 0.5, 1 and 2 mg.

Injection of papaverine outside the crura

In one experiment, papaverine 80 mg was injected near the posterior part of the suspensory ligament, by a needle inserted behind the left spermatic cord. This caused complete anaesthesia of a strip of skin extending along the dorsum of the penis from the root to the beginning of the prepuce, and nearly-complete anaesthesia of a similar strip of dorsal prepuce and dorsal glans. The anaesthesia reached this state within 4 min of the injection. Recovery began 25 min after the injection and was complete by 45 min. There was no erection, and only very slight tumidity (greatest length 11.3 cm) lasting less than 5 min.

In a second experiment papaverine 40 mg was

Table 2 Drugs that cause tumidity but do not consistently cause erection

Drug and dose (mg)	*Date*	*First not flexible 90°*	*First not flexible 20°*	*Not flexible 20° until*	*Not flexible 90° until*	*12 cm long until*
Hydralazine 10	26. 9.83	—	—	—	—	4 min
Hydralazine 16*	1. 7.85	—	—	—	—	(max. 11.9 cm)
Salbutamol 0.1	11. 9.84	—	—	—	—	(max. 11.7 cm)
Salbutamol 0.25	17. 9.84	—	—	—	—	(max. 11.8 cm)
Salbutamol 0.4	15.10.84	—	—	—	—	3 min
Salbutamol 0.4	12. 6.85	2 min	—	—	4 min	6 min
Lignocaine 5	7.11.84	—	—	—	—	21 min
Lignocaine 20	23.11.82	—	—	—	—	25 min
Lignocaine 30	5. 9.84	4 min	—	—	5 min	34 min
Lignocaine 40	26.11.82	—	—	—	—	35 min
Lignocaine 40	18. 3.85	1.5 min	2 min	3 min	3.5 min	28 min
Lignocaine 40	10. 4.85	2 min	—	—	6 min	30 min
Bupivacaine 10	27. 3.85	—	—	—	—	6 min
Bupivacaine 10	10. 4.85	—	—	—	—	13 min

*Blood pressure (sitting) was 130/65 at 5 min and 122/57 at 13 min.
On another day, three sitting blood pressures without drug were 125/70, 129/74 and 126/65, and three during an erection induced by phentolamine were 132/60, 137/56 and 137/73.

injected near the posterior part of the suspensory ligament and 80 mg in the perineum, 40 mg on each side, just superficial to each crus. This caused nearly-complete cutaneous anaesthesia of the whole penis and scrotum lasting about 30 min. There was no erection, and only slight tumidity (greatest length 11.6 cm) lasting less than 5 min.

Discussion

Psychological factors

The very prolonged erection caused by phenoxybenzamine and phentolamine and the very prolonged tumidity caused by guanethidine are entirely undiminished by concentration on exacting intellectual tasks, and it is clear that psychological factors in their causation are negligibly small. With drugs that cause briefer erection or tumidity, the matter is not quite so clear. The conclusion from non-blind experiments that lignocaine has a greater effect in swelling the erectile tissue than bupivacaine was confirmed by the blind comparison of 10.4.85., so this difference is certainly not due to suggestion. Objective indications that psychological factors contribute little to other observations are the ineffectiveness of hydralazine (which I confidently expected would be effective) and

Table 3 Drugs that cause shrinkage of the penis, with subsequent tumidity

Drug and dose (mg)	*Date*	*Least length (cm)*	*< 10.2 cm long until*	*First > 12 cm long*	*Greatest stable length (cm)*	*> 12 cm long until*
Metaraminol 0.2	9.11.84	9.8	40 min	—	11.6	—
Metaraminol 0.2	26. 6.85	9.6	60 min	—	11.9	—
Metaraminol 0.6	11. 2.83	9.7	60 min	—	11.7	—
Metaraminol 1.0	15. 3.83	9.8	80 min	3 h	12.6	6 h
Metaraminol 1.5	1.10.83	9.7	60 min	2.5 h	12.4	7 h
Metaraminol 4	8.11.84	9.5	2.5 h	4.5 h	12.8	9 h
Metaraminol 4	26. 6.85	9.4	3 h	4.5 h	12.7	6.5 h
Guanethidine 1	28. 6.85	10.6	—	2.25 h	12.8	20 h
Guanethidine 2.5	1. 3.83	10.4	—	2.5 h	12.8	20 h
Guanethidine 10	29. 3.83	10.1	30 min	2.5 h	13.0	27 h
Guanethidine 10	6. 5.83	10.4	—	2 h	13.2	25 h
Guanethidine 10	7. 7.83	10.1	30 min	2 h	13.2	20 h
Guanethidine 20	5. 7.85	9.6	95 min	2.5 h	13.2	56 h

Greatest stable length means the greatest length that was equalled or exceeded throughout the whole of a 30 min period.

the fact that during one phentolamine erection I took an urgent and worrying telephone call without losing the erection. On the other hand, attention to involuntary swelling of the penis is somewhat sexually arousing, so a slight or moderate tumidity caused by a drug is almost certainly sometimes increased briefly by the act of measuring it. The erection of 18.3.85. after lignocaine 40 mg (Table 2) may well be of this nature. The fine details of observations on *brief* tumidity or erection must therefore be suspect. In any future research, a way to lessen this inaccuracy is to make every experiment a blind comparison between two drugs or doses, both of which are known to be active. An inactive placebo is useless, because the subject will quickly recognize it as placebo by its failure to cause tumidity.

Comments on surprising results

Hydralazine failed where other smooth muscle relaxants had succeeded. The mechanism of action of this drug is unknown, but it is known that it is much more effective on human forearm arteries than on human hand veins, though these respond equally or with the reverse difference to other drugs (Collier *et al.*, 1978). This suffices to show that it is not a universal smooth muscle relaxant, and one can postulate that the relevant penile smooth muscle is resistant to it.

When I did the first two experiments on imipramine I expected that it would shrink the penis by blocking the re-uptake of noradrenaline, and was very surprised to find that it caused mainly erection and only slight subsequent shrinkage. Before doing the third experiment I had learned of the work of Callingham (1966), who showed that imipramine antagonizes the action of noradrenaline in the sympathetically denervated ear of the rabbit, and at concentrations of 10^{-8} M and above even in the normally innervated rabbit's ear. This makes it almost certain that imipramine is a blocker of α-adrenoceptors, and the only surprise is that in the corpus cavernosum this action seems to predominate (at the doses used) over the better known action of blocking uptake. It is likely that the local anaesthetic action of imipramine plays some part, but it cannot wholly explain the erection from imipramine, since the much more effective local anaesthetic bupivacaine does not cause erection.

Corroborative evidence from patients

Actions like those described in this paper have been observed for phenoxybenzamine (Brindley, 1983b; 1984b; 1986) in impotent and anorgasmic men; phentolamine (Brindley, 1983b, 1986) in impotent men only; thymoxamine and verapamil (Brindley, 1986) in impotent men only; papaverine (Virag, 1982; Virag *et al.*, 1984; Brindley, 1984b; 1986) in impotent and a few anorgasmic men; metaraminol (Brindley, 1984a; Stanners & Colin-Jones, 1984) in men with priapism only; and guanethidine (Brindley, 1986) in impotent men only.

Evidence from these experiments concerning the mechanism of erection

All the drugs which cause erection when given intracavernosally either have no easily visible action on the penis when given systemically, or (phenoxybenzamine and phentolamine: Brindley, 1983b) cause only slight tumidity at doses substantially larger than cause full erection when given intracavernosally. The action must therefore be local, and almost certainly on structures within the cavernosal space. The speed of action makes it difficult to believe that a significant concentration can be reached as far away as the internal pudendal arteries, or even their penile branches, and the failure of large doses of papaverine injected outside the crura to cause erection supports a conclusion that, in those men in whom intracavernosal papaverine or phenoxybenzamine causes prolonged full erection, relaxation of the muscular coat of the internal pudendal and penile arteries (outside the cavernosal space) probably plays no necessary part. Such relaxation, however, may occur under sexual stimulation, and may in some men make the difference between partial and complete erection: in some impotent patients a large dose of papaverine (i.e. 80 mg or 120 mg) or of phenoxybenzamine (i.e. 6 or 10 mg) causes only partial erection, but sexual stimulation during this partial erection makes it complete (Brindley, 1984b; 1986).

The seven drugs that cause erection are all known to be smooth muscle relaxants, acting either on muscle that has α-noradrenergic excitatory innervation (phenoxybenzamine, phentolamine, thymoxamine, imipramine), or on all smooth muscle (papaverine, verapamil, naftidrofuryl). They act in at least three different ways to cause relaxation of smooth muscle, so it is unlikely that there is any action common to all of them except the relaxation of smooth muscle. I have argued elsewhere (Brindley 1984c; 1985) that this smooth muscle is principally of two kinds. One kind constricts intracavernosal branches of the deep penile artery. The other kind, by contracting, opens valves through which blood can flow from the cavernosal space into extracavernosal veins, and when it relaxes these valves close.

Of the two drugs that shrink the penis, metaraminol is an α-adrenoceptor agonist. One would expect that the relevant receptors would be α_1, and this expectation is supported by the failure of idazoxan, a highly selective α_2 blocker, to cause any erection.

Guanethidine is known to cause transient release of noradrenaline from nerve terminals, and then for

many hours abolish such release. If this is its relevant action in the present experiments, we can conclude that the α_1-adrenergically innervated smooth muscle, which by its contraction normally prevents erection, is maintained in its activity partly by noradrenaline released from local nerve terminals. One would expect some activity to be maintained by circulating catecholamines, and the observation that phenoxybenzamine causes prolonged full erection but guanethidine only prolonged tumidity supports this expectation.

The failure of salbutamol to cause more than very slight swelling, and of propranolol to prevent full erection, indicates that β-adrenergic transmission plays no large part in erection.

The failure both of neostigmine to cause any erection, and of atropine to prevent it, were to be expected from the work of Langley & Anderson (1985) for the rabbit, Brindley & Craggs (1975) for the baboon, and Wagner & Brindley (1980) for man. Muscarinic transmission evidently plays no significant part in erection, despite many textbook statements that it is involved.

Practical usefulness

Papaverine and phenoxybenzamine have been useful in treating erectile impotence, and metaraminol in treating priapism. It is likely that they will continue to be useful.

Thymoxamine, phentolamine and verapamil, which cause brief erection, might be used by a surgeon who wishes to see a penis erect to assess its curvature, or by a patient to learn the technique of intracavernosal injection on an occasion when he does not wish his trial to be followed by prolonged erection. Phentolamine is used by Zorgniotti & Lefleur (1985) as a supplement to papaverine.

The long-lasting but weak action of guanethidine could possibly be used in treating some cases of incomplete erectile impotence.

References

BRINDLEY, G.S. (1983a). Cavernosal alpha-blockade and human penile erection. *J. Physiol.*, **342**, 24P.

BRINDLEY, G.S. (1983b). Cavernosal alpha blockade: a new method for investigating and treating erectile impotence. *Br. J. Psychiatr.*, **143**, 312–337.

BRINDLEY, G.S. (1984a). A new treatment for priapism. *Lancet*, **ii**, 220–221.

BRINDLEY, G.S. (1984b). Treatment of impotence by intracavernosal injection of phenoxybenzamine or papaverine. *First World Meeting on Impotence*, Paris, June 1984.

BRINDLEY, G.S. (1984c). The neurophysiology of erection. *First World Meeting on Impotence*, Paris, June 1984.

BRINDLEY, G.S. (1985). Pathophysiology of erection and ejaculation. In *Textbook of Genito-urinary Surgery* ed. Whitfield, H.N. & Hendry, W.F. Edinburgh: Churchill Livingstone.

BRINDLEY, G.S. (1986). Maintenance treatment of erectile impotence by cavernosal unstriated muscle relaxant injection (CUMRI). *Br. J. Psychiat.*, (in press).

BRINDLEY, G.S. & CRAGGS, M.D. (1975). The effect of atropine on the urinary bladder of the baboon and of man. *J. Physiol.*, **256**, 55P.

CALLINGHAM, B.S. (1966). The effects of imipramine and related compounds on the uptake of noradrenaline into sympathetic nerve endings. In *Anti-depressant Drugs*. Proceedings of the 1st International Symposium. ed. Garattini, S. & Dukes, M. pp. 35–43. Amsterdam: Elsevier.

COLLIER, J.G., LORGE, R.S. & ROBINSON, B.F. (1978). Comparison of tolmesoxide (RX 71107), diazoxide, hydrallazine, prazosin, glyceryltrinitrate and sodium nitroprusside on forearm arteries and dorsal hand veins of man. *Br. J. clin. Pharmac.*, **5**, 35–44.

LANGLEY, J.N. & ANDERSON, H.K. (1895). The innervation of the pelvic and adjoining viscera. Part 3. The external generative organs. *J. Physiol.*, **19**, 85–121.

STANNERS, A. & COLIN-JONES, D. (1984). Metaraminol for priapism. *Lancet*, **ii**, 978.

VIRAG, R. (1982) Intracavernous injection of papaverine for erectile failure. *Lancet*, **ii**, 978.

VIRAG, R., FRYDMAN, D., LEGMAN, M. & VIRAG, H. (1984). Intracavernous injection of papaverine as a diagnostic and therapeutic method in erectile failure. *Angiology*, **35**, 79–87.

WAGNER, G. & BRINDLEY, G.S. (1980). The effect of atropine and α-blockers on human penile erection. In *Vasculogenic Impotence*, ed. Zorgniotti, A.W. & Rossi, G. Springfield: C.C. Thomas.

ZORGNIOTTI, A.W. & LEFLEUR, R.S. (1985). Auto-injection of the corpus cavernosum with a vasoactive drug combination for casculogenic impotence. *J. Urol.*, **133**, 39–41.

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