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Maintenance Treatment of Erectile Impotence by Cavernosal Unstriated Muscle Relaxant Injection

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Intracavernosal injection of phenoxybenzamine or papaverine has been tried on 127 men suffering from erectile impotence. In 113 of them it caused an erection which should have sufficed for coitus. Seventy-three men have used such injections, given at home by themselves or their wives, fortnightly or less often, to make coitus possible after each injection; 54 of them still do so.

Virag (1982) reported that injection of papaverine (80 mg) into a corpus cavernosum caused enlargement and stiffening of the penis, and a rise in pressure in the corpora cavernosa of up to 70 mmHg, lasting 10 to 20 minutes. He described using such injections, given every two or three months, as treatment. The purpose was not to enable patients to have sexual intercourse during the artificial erections caused by papaverine, but to achieve benefits lasting from one injection to the next. Such benefits were reported by some patients.

In August 1982, before Virag's work was published but after his discovery had been made, I found in self-experimentation that phentolamine or phenoxybenzamine caused erection when injected into a corpus cavernosum. These erections lasted a few minutes for phentolamine and several hours for phenoxybenzamine. I began almost at once to use phenoxybenzamine as maintenance treatment in erectile impotence, patients learning to inject themselves in order to have sexual intercourse the same day (Brindley, 1983). I became aware of Virag's earlier work on papaverine, and of his subsequent publications (Virag *et al*, 1983, 1984) in November 1983, and began to use papaverine as an alternative to phenoxybenzamine in December 1983.

Zorgniotti & Lefleur (1985) have reported using intracavernosal injection of a mixture of papaverine and phentolamine as maintenance treatment for impotence, and Virag (1985*a*) is now using papaverine in this way.

The general procedure of causing erection by intracavernosal injection of a drug needs a name. The drugs that are known to swell the penis (Brindley, 1986) are phenoxybenzamine and papaverine (both of which give erections lasting for hours, usually complete), phentolamine, thymoxamine, verapamil, naftidrofuryl, lignocaine and imipramine (which give erection, complete or incomplete, lasting a few minutes) and guanethidine (which causes shrinkage of the penis for about the first hour, and then partial erection lasting many hours). All these drugs are relaxants of unstriated muscle. I therefore call the procedure CUMRI (cavernosal unstriated muscle relaxant injection), which has the merit of being easily spoken. The name cavernosal alpha-blockade (CAB), used earlier, was appropriate for phenoxybenzamine but is inappropriate for papaverine. Virag (1985*b*) has recently introduced the abbreviation PIPE (pharmacologically induced prolonged erection). Theoretically this term could be much broader than CUMRI, and could include drugs given by routes other than the cavernosal. As long as no other effective route is known, however, it carries the same meaning apart from excluding the short-acting agents.

The present paper reports the use of CUMRI to investigate 127 men with erectile impotence, and to treat 73 of them.

Table I classifies them by age and principal relevant disabilities. All impotent patients to whom at least one intracavernosal injection of a drug intended to cause erection was given before 31 December 1985 are included.

Technique

Since March 1983 the following procedure has been used. For phenoxybenzamine, 0.04–0.20 ml of the concentrated solution (containing 2–10 mg of the drug) is diluted with 10 ml of saline for doses up to 5 mg, or with 20 ml of saline for doses between 5 and 10 mg. For papaverine, the solution supplied by the manufacturer is undiluted. The dose is 16–120 mg (0.4–3.0 ml).

The injection is delivered through a 16 mm needle of 0.5 mm external diameter into one corpus cavernosum in the proximal third of the free penis. The corpus cavernosum into which the drug has been injected is squeezed firmly for

TABLE I
Present state of patients

	Spinal cord injury or disease[1]				*Other patients*[2]				
Age	*User*	*Former user*	*Non-user*	*Failure*	*User*	*Former user*	*Non-user*	*Failure*	*Total*
20–29	10	1	11	1	1	3	3	1	31
30–39	9	—	3	—	3	1	3	—	19
40–49	6	—	3	1	5	4[3]	3	—	22
50–59	1	—	—	—	8	4	8	5	26
60–69	—	—	—	—	10	5	3	4[4]	22
70–79	—	—	—	—	1	1	3	2[5]	7
Total	26	1	17	2	28	18	23	12	127

1. Spinal cord injury 36, multiple sclerosis 7, spina bifida 1, poliomyelitis 1, paraplegia of obscure origin 1.
2. Mostly with no known relevant disease, but including 3 former alcoholics, 3 men with intermittent claudication, 2 with lesions of the hypogastric plexus, 2 schizophrenics formerly treated with phenothiazines, and 8 diabetics.
3. Includes one patient who died of coronary thrombosis after using CUMRI for 27 months.
4. Includes one patient who died of carcinoma of bladder.
5. Includes one patient who died of carcinoma of the colon.

Both the carcinomas had been diagnosed before the patients received their first injections.

about two seconds along its whole length with the thumbs and fingers of both hands simultaneously, to transfer the drug to the other side. The corpus cavernosum of the other side is then squeezed in the same way. Finally, the penis is pinched transversely with one hand at six or more different places so that the drug reaches both ends of the corpora cavernosa. This massaging procedure after injection is probably important in achieving consistency of effect. Stackl & Bucher (1984), who did not use it, reported failure.

I always give the first injection myself. Some patients lie supine, as a precaution against immediate fainting, but the majority sit for the injection. From the second or third injection the patient (or in a few cases his wife) begins to learn to inject. Patients inject standing or sitting. They are allowed to take a supply of the drug home when they have demonstrated their competence, and are asked to give the injection always in the same part of the penis, so that local fibrosis can be easily detected if it occurs.

I now always try papaverine first. If it gives an adequate erection it is the better drug to use, because side-efects are rarer and the dispensing procedure simpler. If the erection from papaverine is too brief, phenoxybenzamine usually gives more prolonged erection. Before March 1983, injections were made in the middle of the free penis, and the massaging procedure was less thorough. On 10 February 1986, for reasons explained below I ceased using phenoxybenzamine except in one patient.

At present, as a precaution against long-term harm, a limit on the frequency of injections is set at once per fortnight for phenoxybenzamine, and once per fortnight on average (i.e. 26 per year) for papaverine. The reason for making different rules for the two drugs is that there is no refractoriness for papaverine, but phenoxybenzamine works less well on the second of two trials within a few days of each other.

Results

In the majority of both impotent and normal men, CUMRI with phenoxybenzamine or papaverine causes the penis to become fully or almost fully stiff, so that it can be bent to right or to left through no more than 20° (i.e. to no less than 160°). The erection is restricted to the corpora cavernosa; the glans and corpus spongiosum do not swell, or swell very little. Some men develop only poor erections if they lie down to receive the injection and remain lying down, but the erection improves if they stand.

With papaverine, the greatest degree of erection is reached within 4–8 minutes. It commonly stays constant for 1–4 hours, and then subsides completely during 1 hour or less, leaving no obvious after-effect. With phenoxybenzamine, the greatest degree of erection may not be reached until 20 or even 40 minutes after the injection, though in some men it is attained within 10 minutes. It commonly stays constant for 2–6 hours, and then subsides slowly. The penis remains large for at least 24 hours, sometimes 72 hours, and during this period of enlargement erection is often easier to provoke by psychological or mechanical stimulation than before the drug was given.

Table I shows the state of all 127 patients, as known at 1 February 1986. In 113 patients, CUMRI with papaverine or phenoxybenzamine made the penis, for a period of at least 20 minutes, continuously stiff enough to resist bending at the middle of the shaft to 135° (i.e. through 45°) to right and left. This is roughly the threshold for successful coitus. In 14 patients, not even this degree of erection was achieved by CUMRI, though in some of them a larger dose might have succeeded. Failure is significantly more common in older patients. In 40 patients, CUMRI gave a degree of erection that could have allowed coitus, but has not been used at home for this purpose.

TABLE II

Classification of present users by date of first therapeutic use of CUMRI and drug used at 1 February 1986

Drug used at 1 February 1986	*Therapeutic use of CUMRI began*							Total
	Nov. 1982	Jan.–June 1983	July–Dec. 1983	Jan.–June 1984	July–Dec. 1984	Jan.–June 1985	July–Dec. 1985	
Papaverine	—	2	3	4	8	11	6	34
Phenoxybenzamine	1	2	3	5	0	5	1	17
Papaverine and phenoxybenzamine	—	2	—	—	—	—	—	2
Guanethidine	—	—	—	—	—	—	1	1
Total	1	6	6	9	8	16	8	54

Nineteen patients used CUMRI at home for a time, but no longer do so. One of these died suddenly after he had been using CUMRI (always phenoxybenzamine) for 27 months. Necropsy showed myocardial infarction from coronary thrombosis. He was well until a few hours before his death, and had sexual intercourse with the help of CUMRI 5 days before his death. I had palpated his penis 8 weeks before he died, and found it entirely free from lumps. He told me on that occasion that it was straight when erect.

Reasons given for ceasing to use CUMRI have included improvement, so that it was no longer necessary (3 cases); deterioration in the response to the drug (2 cases); loss of sexual partner (2 cases); and implantation of a penile prosthesis (1 case).

At 1 February 1986, 54 patients are still using CUMRI at home. Table II classifies them by drug used and length of use.

Benefits

All patients who have used CUMRI at home say that they have had coitus after every or nearly every injection, though they were always (48 patients) or usually (25 patients) incapable of intromission before treatment began. After papaverine injection, coitus is possible only in the first hour or few hours after injection. Of the 26 patients who have used phenoxybenzamine, 11 say it is often possible on the second, third, or fourth night as well.

No patient who was completely impotent when first seen has reported improvement other than the ability to have coitus in the first few hours (or for phenoxybenzamine the first four days) after an injection.

Among incompletely impotent patients, seven have reported general improvement. Three of these are now ex-users; two are non-users, having improved so much after one or three CUMRI in the clinic that they did not need to use it at home; and two are users, their improvement being insufficient to allow them to do without CUMRI.

Unwanted effects

Pain from the injection

Most patients feel a mild burning pain throughout the penis after injection of either drug. There is little difference in the severity of the pain between the two drugs, but it lasts 10-15 minutes for phenoxybenzamine and less than 2 minutes for papaverine. Accidental subcutaneous injection of phenoxybenzamine causes pain that is more severe than that from intracavernosal injection.

Haematoma

A haematoma, either subcutaneous or under Buck's fascia, appears after a small minority of injections. It is unsightly, but disappears in a few days and causes little pain or discomfort.

Injection into the urethra

A tetraparetic patient with defective penile sensation once accidentally injected papaverine into the urethra. Blood trickled from the meatus for a few minutes, but no other harm was noticed.

Priapism

The duration of action of both drugs is fairly consistent for a given dose in a given man, but it is dose-dependent, and for a given dose varies greatly between men. Priapism, defined as erection lasting continuously for at least 12 hours, has occurred in eleven patients (16 incidents). Some of these have been reported elsewhere (Brindley, 1984). Four incidents resolved spontaneously after 16–26 hours; all the other 12 were successfully treated with metaraminol. The cause was phenoxybenzamine in four incidents and papaverine in 12.

Decrease in the effectiveness of CUMRI

This has occurred in four patients: two using phenoxybenzamine, and two papaverine. In one phenoxybenzamine user the deterioration was slight, but since initially the erection produced by CUMRI was only just adequate for coitus even a slight deterioration made it inadequate, and he ceased to use the procedure. In the other phenoxybenzamine user the deterioration was severe. His erections from CUMRI with phenoxybenzamine were easily adequate for coitus on the first two fortnightly trials, not quite adequate on the third, and not at all adequate on the fourth and fifth. Six months later I did another CUMRI with phenoxybenzamine, and it again caused erection easily adequate for coitus. In the two papaverine users the deterioration was slight, and they continue to use papaverine successfully.

Non-local effects of papaverine

Two patients fainted within a minute of the injection, one of them twice. Both said they had fainted after other injections, and the faints were probably a reaction to the procedure rather than the drug. No other non-penile effects have been reported after papaverine, except for one report of trembling and sweating after 40 mg, though 80 mg had caused no trouble.

Non-local effects of phenoxybenzamine

Even as low as dose as 2 mg may make a patient aware of an increase in nasal resistance to air flow, although some patients deny it, on direct questioning, after 8 mg. Six patients have had evident postural hypotension; one fainted during a meal 3 hours after an injection of phenoxybenzamine (5 mg); one fainted at home after giving himself an accidental overdose, the exact amount being unknown; one fainted at a railway station 2.5 hours after injection (5 mg); and three patients reported minor episodes of feeling faint when standing, relieved by sitting down. The last five of these patients have continued to use the drug, at lower dosage. Three patients have reported dry orgasms, one on all of six trials and the others once each. Urinary incontinence was reported by one patient on two occasions, probably contributed to by his multiple sclerosis. Headaches, lasting several hours, were reported by one patient after each of seven doses of phenoxybenzamine (4 mg) which gave full erection for 2–4 hours. He then changed to papaverine (80 mg) which caused no headache and gave erection that was only slightly less complete and lasted long enough (1 hour). One patient had two episodes of dyspnoea, each lasting 3 minutes, during the first 12 minutes after injection of phenoxybenzamine (5.5 mg).

Local fibrosis

Repeated insertion of needles into any site might be expected to cause local fibrosis, by analogy with the fibrosis that occurs in muscles into which diabetics inject insulin. I recommend that patients always inject into the same part of the penis, to make it easy to detect fibrosis if it occurs. They are asked to feel from time to time for lumps at this site, and I palpate the penis whenever I see a patient, i.e. at 6-monthly or (usually) shorter intervals. Patients are asked also to watch for changes in the curvature of the erect penis. No change in curvature has yet been detected in any patient, but one man, after only nine injections of papaverine, developed palpable firmness close to the injection site. He was placed on a waiting list for a penile prosthesis, and this was implanted in August 1985. The fibrosis found was very slight, and caused no difficulty in implanting the prosthesis.

Theoretical risks not yet observed

Infection

There have been no signs or symptoms of infection after any injection.

Thrombosis

This was to be feared after prolonged priapism, but did not occur. The longest episode of priapism was 40 hours. After this, as after all other episodes, the penis returned rapidly to its normal flaccid size and flexibility. In 10 of the 11 affected patients, full erection occurred subsequently under CUMRI. One patient, who was incompletely impotent, has had no subsequent CUMRI, but he reports that his psychogenic and reflex erections, after being worsened for a few weeks by the episode, recovered and became better than before.

Oncogenesis

Phenoxybenzamine given in large doses by intraperitoneal injection to rats has been reported as causing sarcomata (Flind, 1984). It is approved by the Committee on Safety of Medicines for intravenous injection for very limited indications, but not for the treatment of impotence by intracavernosal injection. The Food and Drugs Administration in the USA does not allow the use of phenoxybenzamine by injection. Recently, further evidence has become available which shows that phenoxybenzamine given orally is carcinogenic in rats (personal communication, Flind, 1986). Consequently, although oral phenoxybenzamine has been in extensive use for many years in man and there has been no evidence of oncogenicity, I have ceased to use phenoxybenzamine for intracavernosal injection except in one patient for whom papaverine gives inadequate erection and who, when I first saw him, had a prostatic carcinoma with metastases.

Papaverine has been little used therapeutically except for CUMRI, and as far as I can discover it has not been subjected to tests of oncogenicity.

Discussion

Most of the users and some of the ex-users have expressed great pleasure at what the treatment has done for them. For a completely impotent man, coitus once per fortnight can be a great improve-

ment on no coitus at all, and for an incompletely impotent man, certainty of successful coitus once per fortnight can be a great improvement on never being certain of success. The fact that 54 men continue to use the treatment shows that they consider the benefits to outweigh the short-term side-effects. Only time will tell whether long-term harmful effects, especially fibrosis, are serious.

Choice and dose of drug

Papaverine is easier for the patient to dispense and has fewer side-effects than phenoxybenzamine. These are sufficient reasons for always trying papaverine first, and using it if it gives adequate erection. However, phenoxybenzamine remains useful in treating a minority of patients, because of its more prolonged action.

One patient gets good erections from 120 mg of papaverine but not from any smaller dose; on the other hand, one patient had priapism after only 18 mg. My present practice is to begin with 16 mg. If this is far from causing adequate erection, the rest of the ampoule (24 mg) is given on the other side 20 minutes later. The dose to be tried at the next consultation is estimated from the degree and duration of erection produced by the 16 or 40 mg given on the first occasion.

From January 1984 to February 1986 I used phenoxybenzamine only for patients in whom papaverine had given erections of insufficient duration. For such patients I began with 4 mg, and was willing to go up to 10 mg if smaller doses gave inadequate erection and no unacceptable side-effects.

Frequency of use

With four patients, I have yielded to their pressure and allowed the limit of 26 injections/year of papaverine to be slightly exceeded. One patient has, with my approval, greatly exceeded the ordinary ration for a single four-week period, but will thereafter not use CUMRI for many months because of his wife's absence. The majority of patients keep close to fortnightly use. A few use CUMRI considerably less often than I tentatively allow as safe. These either have no regular sexual partners or have absent or very defective penile sensation.

Relation between CUMRI and psychotherapy or counselling

Of the 127 patients, 28 have to my knowledge consulted a psychiatrist or psychologist practising sex therapy. They constitute over a third of those patients without spinal cord injury or disease, and none of those with known spinal cord disorders. I have attempted no psychotherapy. I gave brief counselling to a few, but to the majority none at all beyond that which may have been implied by my questions and factual statements.

I hoped, from the first time I tried this treatment, that successful coitus with the help of CUMRI would improve the confidence of many patients in their sexual performance and that this would allow them to succeed without CUMRI. To my disapointment, only seven patients have improved other then after each CUMRI. In this respect my results are far less good than those reported by Virag *et al* (1983, 1984, 1985*a*)

Diagnostic significance of success and failure

If CUMRI causes full erection in an impotent man, this proves that the internal iliac arteries and their relevant branches outside the penis itself are adequate to support full erection when other conditions are favourable. It may not exclude atheroma in these vessels as a contributory factor in the impotence. The success of CUMRI presumably excludes cavernoso-venous or cavernoso-spongiosal shunts as the sole or principal cause of the impotence.

Success, even excellent success, does not exclude total destruction of the preganglionic peripheral nervous pathways of erection. One case establishes this. The patient had a complete flaccid paraplegia below T7 on the right and T6 on the left, following a road accident four years before CUMRI was tried. He had no trace of spontaneous or reflex erections; no lower limb, bulbocavernosus or anal skin reflexes; no tonic glandipudendal reflex (Gillan & Brindley, 1979); and no response of any skeletal muscle in the electroejaculation procedure (Brindley, 1981). Nevertheless, CUMRI with phenoxybenzamine (5 mg caused his penis to stand perpendicular to his trunk, to be flexible only through 10° (i.e. to 170°), and to remain in this state for 70 minutes.

There is no direct evidence as to whether destruction of the postganglionic efferent pathways would prevent successful CUMRI. A theoretical argument suggests that it probably would not: the excitatory innervation of the relevant smooth muscle is mainly α_1–noradrenergic, as the erectile action of α_1–adrenoceptor blockers proves. If the innervation is lost, the α_1–adrenoceptors should continue to be stimulated by circulating catecholamines, and the resulting smooth muscle activity should remain subject to annulment by phenoxybenzamine or papaverine.

Little can be concluded from failure of a single attempt at CUMRI with either drug, since the doses needed by different men differ greatly. If three attempts with increasing doses all fail, one can probably infer that the impotence is due to arterial occlusion or severe stenosis, or to a cavernoso-venous shunt.

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