Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate

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Abstract

Objective—To examine the effectiveness in treating impotence of topically applied cream containing three vasodilators—aminophylline, isosorbide dinitrate, and co-dergocrine mesylate—which act by different mechanisms.

Design—Randomised double blinded placebo controlled crossover trial over two weeks.

Subjects—36 men with erectile dysfunction randomly allocated to two equal groups.

Interventions—Active cream containing aminophylline 3%, isosorbide dinitrate 0.25%, and co-dergocrine mesylate 0.05% for one week and placebo for another.

Main outcome measures—Patients' reported experience of penile responses and side effects of treatment in questionnaires. Penile tumescence and arterial flow in the laboratory.

Results—21 patients reported full erection and satisfactory intercourse with the active cream. Three men reported full erection and satisfactory intercourse with either cream. The active cream was more effective in psychogenic than organic impotence (eight out of nine men with psychogenic impotence achieved a full erection *v* four out of eight with neurogenic impotence and two out of seven with arterial insufficiency). No major side effects were reported. In the laboratory the active cream increased penile arterial flow (0.19 (SD 0.08) m/s *v* 0.02 (0.15) m/s with placebo) and induced tumescence in 24 patients.

Conclusions—Topical treatment with a cream containing three different vasodilators might be considered before intracavernous injection of vasoactive agents, particularly in psychogenic impotence.

Introduction

Current pharmacological treatment for most types of erectile dysfunction is based on the intracorporeal injection of vasoactive agents. These agents either induce erection—for example, papaverine, phenoxybenzamine, and prostaglandin E₁¹⁻⁵—or facilitate it—for example, thymoxamine, phenolamine, nicergoline, dihydroergocryptine, and vasoactive intestinal peptide.^{6,7} Both types of agent need to be injected intracavernously at each use and become less effective with time.⁸ In addition, self injection is painful and stressful and may cause haematoma and infections. Furthermore, intracorporeal fibrosis, priapism, and systemic cardiovascular side effects may develop.⁹⁻¹¹

Topically acting vasodilating drugs seem an attractive option in treating erectile dysfunction, but few studies have investigated the management of impotence by topically effective agents. Most of these reports have described the use of glyceryl trinitrate or minoxidil in the management of erectile dysfunction.¹²⁻¹⁶ Some of them showed a high rate of success¹⁷; most found that glyceryl trinitrate was not useful clinically^{18,19} and that it induced headache at all concentrations used.¹²⁻¹⁹

To our knowledge, topical aminophylline, co-dergocrine mesylate, or isosorbide dinitrate have not been used to

induce or facilitate erection. These agents have variable ability in penetrating the cutaneous tissues, though they are absorbed topically and reach the systemic circulation in small quantities.²⁰⁻²³ We investigated their effectiveness in facilitating erection when given topically in a double blind placebo controlled trial.

Subjects and methods

Patients whose chief complaint was erectile dysfunction were invited to participate in the present study. Their median age was 48 (range 31-65). The median duration of erectile dysfunction was 39 months (range 5-72). The cause of the dysfunction was determined after the initial evaluation and consultation, which included serum testosterone determination, neurological and psychiatric evaluation, penile blood flow assessment by colour duplex ultrasonography, and a papaverine test.^{24,25} Medical history associated with erectile dysfunction was variable (diabetes mellitus, hypertension, anxiety, depression, and surgery). No patient with hypotension or glaucoma was enrolled in this study.

Two weeks after the papaverine test each patient was informed that he would be asked to determine which of two different treatments was the more useful. One cream contained a combination of aminophylline 3%, co-dergocrine mesylate 0.05%, and isosorbide dinitrate 0.25% (active cream) and the other lubricating gel (placebo). The two creams were prepared in the hospital's pharmacology department for research purposes. Patients attended the urology outpatients clinic at the hospital and gave their informed consent to participate in the study. They were classified into two strata according to age. They were randomly allocated to two groups by means of a stratified systematic random technique, the first patient in each stratum who attended the clinic being in group I, the next in group II, and so on, until each group contained 18 patients. Each group received the active and placebo creams alternately, one preparation each week. In the first week group I received the treatment cream and group II the placebo. In the second week group I received placebo cream and group II the treatment cream. Investigators were blind to which cream was being used by means of coded labels. The two preparations looked similar and had identical packaging. Each patient was given seven divided doses of 2 g of cream (on the basis of one dose daily).

Penile tumescence and arterial flow were measured in the laboratory before and after each week's trial of a cream. No erotic stimulation was used during these laboratory measurements. Before the trial patients were advised to apply a thin layer of cream on the glans penis and on the penile shaft 15 minutes before erotic stimulation and intercourse at home. Patients with venous leakage were advised to use a tourniquet at the base of the penis. Cream was applied to the glans penis as well as the shaft to enhance transcutaneous absorption of active ingredients.¹⁶

Patients reported their experience after each week in a questionnaire. The questionnaire investigated three main areas: erectile response, patient's satisfaction, and side effects. Each patient described all his experiences

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BMJ 1996;312:1512-5

Table 1—Penile response after topical application of placebo and active creams in 36 patients with erectile dysfunction. Values are numbers of patients

Aetiology	Response			
	Full erection	Partial erection	Tumescence	No response
Placebo cream				
Psychogenic (n = 9)	3			6
Neurogenic (n = 8)				8
Arterial insufficiency (n = 7)				7
Venous leakage (n = 4)				4
Mixed* (n = 8)				8
Total (n = 36)	3			33
Active cream				
Psychogenic (n = 9)	8			1
Neurogenic (n = 8)	4	1	1	2
Arterial insufficiency (n = 7)	2	1	1	3
Venous leakage (n = 4)	1			3
Mixed* (n = 8)	6			2
Total (n = 36)	21	2	2	11

* Psychogenic with minor organic disorder.

over the week, but the best response during the week was used in the statistical analyses. Erectile response and patient's satisfaction were measured on seven point semantic scales.⁸ Erectile response was graded as full erection, which implies successful intercourse; partial erection, in which penetration but not intercourse is possible; tumescence, in which penetration is not possible; and no response.

Statistical analysis included Student's *t* test (peak flow velocity) and χ^2 test (erectile response) for comparison of the two groups (unpaired data), and it included paired *t* tests (peak flow velocity) and McNemar's test (erectile response) for analysis of data in each group (paired data). McNemar's test was used to compare the proportions of men with full erections.

Results

During laboratory testing active treatment was highly effective in increasing penile arterial flow (figs 1 and 2). Mean arterial flow with active treatment was 0.06

Fig 1—Duplex ultrasonogram showing good peak flow velocity (0.34 m/s) after application of active cream in patient with arterial impotence

(SD 0.02) m/s before application and 0.25 (0.10) m/s after application ($P<0.001$), compared with 0.06 (0.02) m/s before and 0.08 (0.07) m/s after application of placebo ($P>0.05$). Moreover, the active treatment caused tumescence in 24 patients, the tumescence being complete in seven and partial in 17. No tumescence was achieved in 12 patients.

Analysis of data from the questionnaires showed that the active cream induced a greater erectile response than did placebo (21 v 3, $P<0.001$). The response after the active cream was significantly different from that before application (21 v 0, $P<0.001$ by McNemar's test), while the response after placebo was no different from that before application (3 v 0, $P = 0.25$ by McNemar's test).

The penile response after placebo and active treatment is shown in table 1. Twenty five patients reported spontaneous erections during the week of active treatment. The quality and duration of erection varied. Twenty one patients reported a full erection with successful intercourse, orgasm, and ejaculation. Eight of them had a full erection after the first application, while six, four, and three patients respectively reported a full erection after two, three, and five days of using the cream once daily. Other respondents were dissatisfied; two had a partial erection that was insufficient for successful intercourse and two had tumescence without sufficient rigidity for intercourse.

Fig 2—Duplex ultrasonogram showing a weak response in peak flow velocity with placebo (0.09 m/s) and active cream (0.22 m/s) in diabetic patient with arterial, neurogenic, and psychogenic impotence over previous five years

Erectile dysfunction of psychogenic origin or of mixed causes (mostly minor neurological or arterial in addition to psychogenic disorders) was most successfully treated by the active cream. Only one of the four patients with venous leakage had a good response, and he used a tourniquet 20 minutes after applying the cream. The active cream was more effective in neurogenic impotence (four out of eight patients had a full erection) than in arterial impotence (two out of seven patients had a full erection) (table 1).

Three of the nine patients with psychogenic impotence described a full erection and satisfactory intercourse with both types of cream. Neither cream produced a noticeable response in 11 patients (table 1).

None of the patients had prolonged erection or priapism. None of them reported clinically significant cardiovascular side effects (such as postural dizziness), headache, or pain at site of application. None of them reported complaints from their partner.

Discussion

The active cream acts locally on penile tissue. If the topical application of cream precedes sexual intercourse, the release of neurotransmitters prompted by erotic stimulation will enhance further the action of the pharmacological agents and result in a better erection.²⁴ For these reasons none of the 36 patients achieved a full erection in our laboratory, whereas 21 of them had a full erection during sexual intercourse. The greatest effect was seen in psychogenic impotence with or without a neurogenic disorder and the lowest in vascular impotence. This may be because the agents in the active treatment are primarily vasodilators and penile vasculature is healthy in psychogenic impotence but compromised in vascular impotence.

PHARMACODYNAMICS OF AGENTS IN ACTIVE CREAM

Papaverine works better when it is injected in combination with phentolamine to induce erection.^{3 8 10} The two drugs act by different mechanisms, so we combined three agents with different mechanisms of action in our active cream.

Aminophylline releases theophylline after crossing the skin. Theophylline induces erection on intracavernous injection²⁶ and acts similarly to papaverine. It inhibits the action of phosphodiesterase, thus preventing the breakdown of cyclic AMP to 5-AMP and subsequently causing sinusoidal smooth muscle relaxation and erection.²⁷

Agents such as isosorbide dinitrate are absorbed topically and generate nitric oxide either spontaneously or after metabolism in smooth muscle. Nitric oxide activates guanylate cyclase and the formation of cyclic GMP (guanosine monophosphate), causing local relaxation of corporeal smooth muscle. This results in increased filling of the corpus cavernosum with blood and consequently impairment of venous outflow, thereby causing penile erection.^{14 27 28}

Current data suggest that selective blockade of α adrenergic nerve impulses within the corpus cavernosum in impotent men will promote erection. Erection was produced by intracavernous injection of phenoxybenzamine in six out of 11 impotent men,¹ while lower activity was reported with phentolamine.²⁹ However, dihydroergocryptine (one component of co-dergocrine) was effective only as a facilitator of erection.^{6 7} In a previous study co-dergocrine cream elicited full erection in 22% of impotent men after erotic stimulation.³⁰ Co-dergocrine has blocking activity at α receptors and also has central actions,³¹ which may contribute to its valuable effect on erectile dysfunction.

CONCLUSIONS

During laboratory testing the active cream significantly increased penile arterial flow and induced

Key messages

- Impotence is almost routinely treated by vasoactive drugs given by intracavernous injections, which may be stressful for patients and have unpleasant side effects
- In this study a topical cream containing three vasodilators with different mechanisms of action was tested in a double blind placebo controlled crossover trial in 36 impotent men
- The active cream increased penile arterial flow and induced tumescence in the laboratory, and 21 patients reported full erection and intercourse after a week's treatment
- The cream was most effective in psychogenic impotence, success rates being lower when the impotence had organic causes
- This topical treatment should be used before intracavernous agents, especially in psychogenic impotence

tumescence in 66% of patients. Tumescence under laboratory conditions may be an index of erection on erotic stimulation during sexual activity. We can draw several conclusions from the laboratory data and the data obtained after erotic stimulation at home. A combination of aminophylline, co-dergocrine, and isosorbide dinitrate, even in the small doses of our active cream, was as effective in treating impotence as the reported intracavernous injection of vasoactive agents.¹⁻⁵ The cream had no clinically significant side effects. Headache was not reported by any patient because the dose of isosorbide dinitrate in the cream was smaller than the usual systemic dose.

Even though more studies are needed, topical treatment of impotence with a cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate might be considered before the intracavernous injection of vasoactive drugs.

Funding: No additional funding.

Conflict of interest: None.

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(Accepted 6 March 1996)

Certification of cause of death in patients dying soon after proximal femoral fracture

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Certification of cause of death has been a legal obligation for medical practitioners since 1874¹ and has been central to our knowledge of the incidence of fatal diseases. To assess whether certified cause of death reflects the well documented high mortality after fracture of the proximal femur,² we reviewed the certification of cause of death in patients who died soon after such injuries. If a fracture is mentioned on the death certificate as contributory to death the registrar of deaths has a duty to report it to the coroner and the coroner must hold an inquest. We suspected that the need for an inquest might act as a barrier to doctors recording fractures on the death certificate.

Patients, methods, and results

We collected data prospectively in 1991-2 on patients admitted to Leicester Royal Infirmary with proximal femoral fractures who died within 28 days of admission to see what was recorded on their death certificate and whether or not a coroner's inquest was held. No calculation of sample size was performed because we had no idea of expected differences.

Ninety four of 1274 consecutive patients with fractures died within 28 days; the cause of death on the death certificate was obtained for 92 of these patients (98% follow up). An inquest was held in 22 of the 92 cases (23%); every case was checked with hospital data sources and referenced to the death certificate and information from the coroner's office. In each of these 22 cases the fracture was recorded on the death certificate as a contributory factor. In only one out of the 70 cases where an inquest was not held, however, was the fracture recorded on the death certificate (and in that case an inquest was not indicated because it was a pathological fracture). No certificate recorded the fracture as being the direct cause of death. The difference between the two groups in hip fracture appearing on the death certificate was highly significant ($P < 0.001$ by χ^2 test with Yates's correction; 95% confidence interval 0.00 to 0.01).

Comment

In most patients who die within 28 days of admission for hip fracture the fracture contributes significantly to death—for example, through problems related to immobility—even though the direct cause may be a medical problem such as bronchopneumonia. This judgment was the initial reason for choosing 28 days as the cut off point for this study and was supported by the coroner's finding in every case in which an inquest was held that the fracture had been contributory. There is no specified interval for the reporting of trauma related deaths to the coroner, but junior hospital staff often use 28 days or four weeks as a rule of thumb.

Twenty three per cent may seem a high proportion of proximal femoral fractures to necessitate an inquest, but these deaths are early in the period after injury. Deaths occurring later, when the importance of the fracture becomes less, will rarely involve the coroner, and the overall proportion will therefore be much lower. The inquest is a formality necessitated by the mention of the fracture on the death certificate and is in addition to the coroner's post mortem examination.

The practice of not mentioning the fracture on the death certificate to avoid an inquest may lead to considerable under certification of proximal femoral fracture as a predisposing cause of death—75% of cases were unreported in our series. This has been recognised before, and true mortality figures have to be estimated in an unsatisfactory empirical fashion.³ A legal facility to mention age related proximal femoral fractures on the death certificate without the mandatory need for an inquest may improve the accuracy of mortality figures.

Funding: Collection of data for this study was aided by funding from the Wishbone Trust.

Conflict of interest: None.

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(Accepted 2 February 1996)

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BMJ 1996;312:1515