The substitution of Phentolamine with an equal amount of Chlopromazine as an alpha-blocker in vasoactive cocktails used for intracavernous injection therapy for the treatment of erectile dysfunction

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Abstract

Introduction

This brief report describes the replacement of phentolamine mesylate with an equal amount of chlorpromazine HCl in vasoactive drug mixtures used as intracavernous (IC) injection therapy for treating erectile dysfunction (ED). Phentolamine, amongst other drugs, had been used in drug injection therapy for the treatment of ED, but was replaced as single drug therapy by more effective drugs, such as alprostadil (prostaglandin E1). It has, however, still widely been used as alpha-blocking agent in vasoactive drug cocktails. Phentolamine has a synergistic effect with alprostadil, papaverine and atropine in drug combination cocktails. These injection mixtures are very effective for treating ED and are commonly known as bimixtures, trimixtures and quadmixtures. The vasoactive drug, phentolamine, was withdrawn from the market in South Africa. Chlorpromazine (a phenothiazine) was suggested as an alternative alpha-blocking agent to be used in drug cocktails for the IC treatment of ED.

Methods

Three hundred and sixty-four (364) patients were questioned and evaluated during follow-up visits to an ED clinic after phentolamine mesylate was replaced with an equal amount of chlorpromazine HCL in their regular IC injection preparations. The collected data is based on results from self-administration at home.

Results

No significantly unusual adverse effects or altered efficacy of the new preparations were reported. The patients noted a change in the colour of the drug mixtures that contain chlorpromazine and papaverine. Despite this slight change in colour, the effectiveness of the mixtures remained the same if a use-before date of three months was adhered to.

Conclusion

The results indicate that phentolamine mesylate can effectively be replaced with an equal amount of chlorpromazine HCL in IC drug cocktails for the treatment of ED.

SA Fam Pract 2007;49(1):14

The full version of this article is available at: www.safpj.co.za

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Materials and Methods

Three different vasoactive preparations, namely a bimixture, trimixture and quadmixture, were compounded. The three different mixtures were dispensed to patients at three different clinics treating patients with ED. The sterile mixtures were prepared by qualified pharmacists under aseptic conditions in a class 100 laminar airflow cabinet in a class 100 air quality clean room environment. The drugs were mixed and diluted to the correct final concentration with sterile normal saline (NaCl 0.9%, Adcock Critical Care, South Africa).The mixtures that were compounded contained exactly the same concentration of chlorpromazine HCL (Largactil, Aventis Pharma, South Africa) instead of the previously used phentolamine mesylate (Regitine, Novartis, South Africa). The bimixture contained alprostadil (Cascade Biochem, Little island, Cork, Ireland) 10 µg/ml and chlorpromazine HCl 0.4 mg/ml. The trimixture contained alprostadil 20 µg/ml, chlorpromazine HCL 1 mg/ml and papaverine HCL (Papaverine 60, Aspen Pharmacare: Pharma, South Africa) 12 mg/ml. The quadmixture contained alprostadil 10 µg/ml, chlorpromazine HCL 1 mg/ml, papaverine HCL 12 mg/ml and atropine sulphate (Atropine Sulphate-Fresenius Amps, Fresenius Kabi, Bodene, South Africa) 0.15 mg/ml.

The mixtures were dispensed to patients in either 1 or 0.5 millilitre unit dose insulin syringes (BD Micro-Fine Plus, Beckton Dickenson and Company, Franklin Lakes, NJ, USA) or in sterile 10 millilitre glass multi-dose injection vials (Anchor Rand, Johannesburg, South Africa), depending on the patient's requirements. All patients had previously been treated with phentolamine mesylate combined with the other drug(s) in the same mixtures for at least three months or longer prior to the changeover to chlorpromazine HCl mixtures. The patients were asked to store the medication in a refrigerator in exactly the same way as before, to inject exactly the same volume as before and not to deviate from any personal procedures that they have been accustomed to with the use of the previous preparations. A beyond-use date of three months if stored at 5°C was maintained. This was done because of the limited stability of alprostadil in solution,[17,18] although increased stability of compounded IC cocktails have been reported after the preparations were subjected to a number of freeze-thaw cycles.[19] The patients were informed about the drug substitution. During the follow-up visits of the patients to the clinics, they were asked to report (yes or no) in a simple questionnaire on the effectiveness of the drug or on side effects not previously noted with the phentolamine preparations. The questions included (a) burning sensation - not previously experienced after injection, (b) prolonged or insufficient erections, (c) lump formation, (d) effects related to abnormal systemic fall in blood pressure, (e) changes in effectiveness of the new medication, (f) physical changes in the drug preparation itself (e.g. colour, viscosity, crystallisation, etc.) and (g) satisfaction with the new preparation.

In the cases where positive answers to the questions (yes answer) were reported, more information regarding those questions and answers were asked and noted by the clinician.

Results

Table I shows the reported effects or side effects of compounded chlorpromazine cocktails.

a. *Burning sensation - not previously experienced after injection.
b. Prolonged or insufficient erection.
c. Lump formation.
d. Effects related to abnormal systemic fall in blood pressure.
e. Changes in efficacy of the medication.
f. Physical changes in the preparation itself (e.g. colour, viscosity, crystallisation, etc.).
g. Satisfaction with the new preparation.

A burning sensation caused by IC injections that contain alprostadil is a common side effect. Only one patient (0.33%) in the bimix group reported a difference regarding this effect (a). Prolonged or insufficient erections (b) were reported by two patients (0.65%) using bimix, by one patient (3.03%) using the trimix and by one patient (3.85%) in the quadmix group. No lump formation (c) and other effects related to abnormal systemic fall in blood pressure (d) were reported with any of the preparations. Changes in the efficacy of the medication (e) were reported by two patients (0.65%) in the bimix, two (6.06%) in the trimix and one (3.85%) in the quadmix group. Physical changes in the preparation (f) were reported by 31 patients (93.94%) in the trimix group and 23 (88.46%) in the quadmix group. Two hundred and ninety-eight (97.70%), 29 (87.88%) and 24 (92.30%) patients in the bimix, trimix and quadmix groups respectively were satisfied with the new preparations (g).

In all cases in which patients (1.10%) reported prolonged or insufficient erections (b), it was due to insufficient erections rather than prolonged erections. All the patients that reported changes in medication efficacy (e) (1.37 %) did so because of an improvement in the effectiveness of the new preparation. A colour change (f) in the new preparation was reported by 93.94% of patients on the trimix preparations and by 88.46% of patients on the quadmix preparations. Both these preparations contain chlorpromazine and papaverine. The bimix (alprostadil and chlorpromazine) remained clear, as with the previous phentolamine preparations.

Conclusion

Although the data collected for our study was based on self-administration at home, our results correlate with those obtained in a controlled clinic setting[16] and clearly indicate that phentolamine mesylate can effectively be replaced with chlorpromazine HCL in IC injection

Table I: Reported effects / side effects of compounded chlorpromazine cocktails

	Vol. (ml)	Num. of patients	Av. Vol./ Patient (ml)	Positive responses (yes answers) to evaluation questions*						
				(a)	(b)	(c)	(d)	(e)	(f)	(g)
Bimix	916	305	3.0	1 (0.33%)	2 (0.65%)	0	0	2 (0.65%)	0	298 (97.70%)
Trimix	32	33	4.0	0	1 (3.03%)	0	0	2 (6.06%)	31 (93.94%)	29 (87.88%)
Quadmix	104	26	4.0	0	1 (3.85%)	0	0	1 (3.85%)	23 (88.46%)	24 (92.30%)
Total	1152	364	3.6	1 (0.27%)	4 (1.10%)	0	0	5 (1.37%)	54 (14.84%)	351 (96.43%)

cocktails for the treatment of ED. At the same concentration, the efficacy and adverse effects are similar to that of phentolamine mesylate. No lump formation and postural hypotension were reported. The change in colour of the compounded mixtures containing chlorpromazine and papaverine was the most noted difference in these preparations. The yellowish colour remains stable if the preparation is stored at 5 °C in the dark for up to three months and does not seem to influence the effectiveness of the compounded mixtures. The effects of long-term use of chlorpromazine HCL in IC injections and its combination with oral agents still needs to be investigated.

Acknowledgements: Dr W Bestane and Dr C Jardim of the Department of Urology, Ana Costa Hospital, Santos SP, Brazil, for communicating their experience regarding this subject.

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