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 The vasoactive drug, phentolamine, was withdrawn from the market in South Africa.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

This article has been peer reviewed.
Materials and Methods
Three different vasoactive preparations, namely a bimixture, trimixture and quadmix- 
ture, were compounded. The three dif- 
ferent mixtures were dispensed to pa- 
tients 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 
ads were mixed and diluted to the 
correct final concentration with sterile 
water normal saline (NaCl 0.9%, Adcock Crit- 
cal Care, South Africa). The mixtures that 
were compounded contained exactly the 
same concentration of chlorproma- 
zine HCL (Largactil, Aventis Pharma, 
South Africa) instead of the previously 
used phentolamine mesylate (Regitine, 
Novartis, South Africa). The bimixture 
employed alprostadil (Cascade Bio- 
chem, Little island, Cork, Ireland) 10 
µg/ml and chlorpromazine HCI 0.4 mg/ 
ml. The trimixture contained alprostadil 
20 µg/ml, chlorpromazine HCL 1 mg/ml 
and papaverine HCL (Papaverine 60, 
Aspen Pharmcare: Pharma, South 
Africa) 12 mg/ml. The quadmixture 
employed alprostadil 10 µg/ml, chlor- 
promazine 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 insu- 
lin syringes (BD Micro-Fine Plus, Beck- 
ton Dickenson and Company, Franklin 
Lakes, NJ, USA) or in sterile 10 millitre 
glass multi-dose injection vials (Anchor 
Rand, Johannesburg, South Africa), de- 
pending 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 chlor- 
promazine 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 vol- 
ume 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 solu- 
tion.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 ef- 
effects not previously noted with the phen- 
tolamine 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 pres- 
sure, (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 chlor- 
promazine 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 medica-
tion.
[f] Physical changes in the preparation 
itself (e.g. colour, viscosity, crystal-
лизация, etc.).
[g] satisfaction with the new prepara-
tion.

A burning sensation caused by IC 
 injecions that contain alprostadil is a 
common side effect. Only one patient 
(0.33%) in the bimix group reported a 
difference regarding this effect (a). Pro- 
longed 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 medica-
tion (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 prepa-
ration (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 erec-
tions (b), it was due to insufficient erec-
tions 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 prepara-
tions. 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 setting16 
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

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

References