ORIGINAL RESEARCH

BETHANECOL CHLORIDE FOR TREATMENT OF CLOMIPRAMINE-INDUCED ORGASMIC DYSFUNCTION IN MALES

Márcio Bernik, Antonio Hélio Guerra Vieira and Paula Villela Nunes


PURPOSE: To investigate whether bethanecol chloride may be an alternative for the clinical management of clomipramine-induced orgasmic dysfunction, reported to occur in up to 96% of male users.

METHODS: In this study, 12 fully remitted panic disorder patients, complaining of severe clomipramine-induced ejaculatory delay, were randomly assigned to either bethanecol chloride tablets (20 mg, as needed) or placebo in a randomized, double-blind, placebo-controlled, two-period crossover study. A visual analog scale was used to assess severity of the orgasmic dysfunction.

RESULTS: A clear improvement was observed in the active treatment period. No placebo or carry-over effects were observed.

CONCLUSION: These findings suggest that bethanecol chloride given 45 minutes before sexual intercourse may be useful for clomipramine-induced orgasmic dysfunction in males.


In panic disorder patients, effective pharmacological treatment with antidepressants has been shown to greatly improve the quality of life, but it is often associated with the emergence of sexual dysfunctions.1

Sexual dysfunctions are common2-4 but systematically underreported side effects.5,6 They are, nonetheless, associated with noncompliance, leading to early treatment dropout, treatment nonresponse, and relapse of symptoms.4,7

Among the antidepressants, serotonin selective reuptake inhibitors (SSRIs) and clomipramine, may cause more sexual side effects than other antidepressants.6,8,9,10 Biochemical mechanisms suggested as causative include the following: 1) increased brain serotonin, particularly affecting 5TH2 and 5HT3 receptors; 2) decreased dopamine; 3) central blockade of cholinergic and alpha-1 adrenergic receptors; 4) inhibition of nitric oxide synthetase; 5) elevation of prolactin levels; and 6) peripheral muscarinic blockade.11

Clomipramine is considered the gold standard for treatment of panic disorder.12 On the other hand, its use is commonly associated with sexual side effects such as orgasmic dysfunction in up to 20% to 96% of patients.5,6,13

Clomipramine is the imipramine analogue of chlorpromazine. Compared to other tricyclic antidepressants (TCA), it has a greater effect upon dopamine blockade and serotonin uptake inhibition.14 This has implications for prolactin release15 and orgasmic dysfunction mediated through 5HT2 receptors.16 Moreover, peripheral antimuscarinic17 and alpha-adrenergic blockade7,18,19 effects have also been implicated in the mechanism of clomipramine-induced orgasmic dysfunctions.

There are few studies of the clinical management of antidepressant-in-
duced sexual dysfunctions. Case reports and open trials suggested that yohimbine,20 bupropion,21 cyproheptadine,22 sildenafil citrate,10,23 buspirone,6 and bethanecol chloride24-26 may be effective in antidepressant-induced sexual dysfunctions.

Bethanecol chloride has mixed central and peripheral cholinergic and adrenergic effects. When used in doses of 10 to 100 mg given 30 to 60 minutes before intercourse, it has been suggested in case reports to be effective in reversing antidepressant-induced anorgasmia.24-26 The supposed mechanism of action is the muscarinic agonist-induced potentiation of adrenergic function.17

In this study, we further investigated the efficacy of bethanecol for the treatment of clomipramine-induced orgasmic dysfunction in male patients using clomipramine as maintenance treatment for panic disorder in a randomized, double-blind, placebo-controlled, crossover trial.

METHODS

Twelve panic disorder patients (all male) aged 18 to 65 years gave informed consent to take part in this study. The duration of the orgasmic dysfunction (ejaculatory delay or anorgasmia) was 5.8 ± 5.8 (mean ± standard deviation) months. No patient complained of erectile dysfunction.

All patients were fully remitted and were receiving clomipramine as maintenance treatment. The mean daily dose of clomipramine was 106 ± 64 mg (range: 30 - 200 mg), and the duration of treatment was 6.9 ± 5.4 months (range: 1 - 18 months). Subjects using other medications were excluded.

Inclusion criteria were absence of sexual dysfunction prior to clomipramine use, presence of normal sexual desire; absence of medical illness or use of other drugs known to interfere with sexual functioning; and no personal history of asthma, coronary insufficiency, or duodenum ulcer.

Subjects were assigned to receive either bethanecol chloride tablets (20 mg, as needed) or placebo in a randomized, double-blind, placebo-controlled, two-period crossover study (Group A = bethanecol 2 weeks/ placebo 2 weeks; Group B = placebo 2 weeks / bethanecol 2 weeks). Patients were given either 2 capsules of 20 mg bethanecol or 2 of placebo in each period and were instructed to take the medication 45 minutes before sexual intercourse on up to 2 occasions in each 2-week period. Additional tablets were not provided. In order to avoid absorption delays, subjects were instructed to wait 2 hours after full meals.

Patients were evaluated at baseline and at week 2 and 4.

Baseline measures included the Hamilton Depression Rating Scale (HDRS27), Hamilton Anxiety Scale (HAS28), and a visual analog sexual function scale constructed with 6 anchor points (Table 1). Even though this scale measures both erectile and ejaculatory (orgasmic) function, only the orgasmic function measures were analyzed as there were no predicted effects of both clomipramine and bethanecol on erectile functioning.

The best scores of orgasmic function in the placebo and drug phases of patients completing the study were compared using a version of the Wilcoxon rank sum test, corrected for small samples.29 A significance level of 5% was adopted.

RESULTS

Two patients dropped out of the study before the second period of treatment; 1 relapsed to a depressive episode, and the other could not adapt his sexual habits to bethanecol chloride use. We analyzed the data on the 10 subjects who completed the study.

The baseline scores on the psychopathological rating scales were HAS (6.9 ± 3.8) and HDRS (5.7 ± 3.9). Table 2 shows the individual scores at baseline, placebo, and bethanecol periods. A clear improvement over baseline was observed in the orgasmic functioning of patients during the active treatment period with bethanecol. (W = 62; P < .025). No carry-over or placebo effects were observed.

Given the small sample size, we could not correlate the effects of bethanecol effects with clomipramine dose levels or to the baseline severity of orgasmic dysfunction.

Table 1 - Visual analog sexual function scale, anchor points.

<table>
<thead>
<tr>
<th>SEXUAL FUNCTION SCALE</th>
<th>I) Which of the statements below best describes your erection during intercourse.</th>
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</thead>
<tbody>
<tr>
<td>1-1 had no erection.</td>
<td>2-I had some erection, but not enough to penetrate.</td>
</tr>
<tr>
<td>3-Loss of erection during or at the beginning of sexual intercourse.</td>
<td></td>
</tr>
<tr>
<td>4-Loss of the erection at the end of intercourse due to tiredness.</td>
<td></td>
</tr>
<tr>
<td>5-Difficulties in keeping the erection during intercourse but could finish it.</td>
<td></td>
</tr>
<tr>
<td>6-Normal erection, as used to be.</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>II) Which of the statements below best describes your effort to reach orgasm (ejaculation):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-No orgasm.</td>
</tr>
<tr>
<td>2-Had an orgasm with extreme effort and tiredness.</td>
</tr>
<tr>
<td>3-Clearly needed more effort and concentration.</td>
</tr>
<tr>
<td>4-Moderate effort and more time needed to reach orgasm than normally needed.</td>
</tr>
<tr>
<td>5-Noted some delay or difficulty, almost normal.</td>
</tr>
<tr>
<td>6-Usual time and effort needed to reach an orgasm.</td>
</tr>
</tbody>
</table>
DISCUSSION

The small sample size imposes limits on the generalization of the present results. Nevertheless, we found an improvement in the patients sexual functioning after bethanecol. This effect was not related to psychopathological changes or clomipramine dosing changes during the study. In fact, all patients were in remission and on maintenance doses during this trial.

The mechanism of action of bethanecol is still not fully understood. It has been proposed that an imbalance between cholinergic and adrenergic function is responsible for tricyclic antidepressant-induced orgasmic dysfunction.17 These authors hypothesized a muscarinic agonist-induced potentiation of adrenergic function as an explanation for the effects of bethanecol. In fact yohimbine, an alpha-2 adrenergic antagonist, was also shown to reverse clomipramine-induced anorgasmia.20 More recently, bupropion, which also promotes central adrenergic potentiation, has also been shown to be useful in SSRI-induced sexual dysfunction.30 On the other hand, mazindol, an anorectic drug that increases sympathetic tonus, provokes anorgasmia that was reversed by bethanecol.25

We conclude that bethanecol chloride may be a valid option in the treatment of clomipramine-induced orgasmic dysfunction.

ACKNOWLEDGMENTS

The authors thank Cristiane Pinheiro Lima, for editorial assistance and Marcus Estanislau, for statistical analysis.

Table 2 - Individual data on the orgasmic functioning scale, score at baseline and best score at each treatment period.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Clomipramine dose</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Bethanecol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>30 mg</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>175 mg</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>75 mg</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>40 mg</td>
<td>2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>50 mg</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>75 mg</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>200 mg</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>75 mg</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>50 mg</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>150 mg</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

REFERENCES


RESUMO


OBJETIVO: Investigar se o uso do cloridrato de betanecol é uma alternativa útil no manejo clínico da disfunção orgástica induzida pela clomipramina, relatada por até 96% dos usuários do sexo masculino.

MÉTODOS: Foram estudados 12 pacientes do sexo masculino em remissão completa de transtorno de pânico porém com queixas de disfunção orgástica grave secundária ao uso da clomipramina. Os pacientes foram aleatoriamente distribuídos ao tratamento com cloridrato de betanecol (20 mg quando necessário) ou placebo em um estudo duplo cego “crossover” de dois períodos.

RESULTADOS: Foi observado um benefício claro no período de uso da droga ativa. Não foram observados efeito placebo ou “carry-over” nos pacientes inicialmente alocados ao medi-camento ativo.

CONCLUSÕES: Os resultados deste estudo sugerem que o cloridrato de betanecol, usado em doses únicas, 45 minutos antes da relação sexual, pode ser útil em pacientes do sexo masculino apresentando disfunção orgástica secundária ao uso da clomipramina.

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