Randomized placebo controlled trial of lofexidine hydrochloride for chronic pelvic pain in women

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BACKGROUND: We hypothesised that the orally-active α₂-adrenoceptor agonist lofexidine hydrochloride would ameliorate chronic pelvic pain in women. METHODS: A randomized placebo-controlled parallel group trial was undertaken in the University Hospital Gynaecology Clinic. Women with pelvic pain of at least 6 months duration were eligible, and were randomized using a sealed envelope system to receive up to 600 mg lofexidine hydrochloride twice daily over 8 weeks or placebo. Outcome measures were summary and daily diary visual analog scales for pain (VAS) and a 5 point self rating scale. RESULTS: 9/19 women randomized to lofexidine completed the study compared to 14/20 of those randomized to placebo. Intention-to-treat analysis showed that 4/19 in the lofexidine group achieved 50% or greater reduction in VAS compared with 8/20 in the placebo group (OR 2.5, 95% CI 0.6–10.3). Summary and diary VAS were closely correlated. CONCLUSIONS: Within the limits of a small study with power to detect only a substantial effect, we conclude that lofexidine hydrochloride is not effective for the treatment of chronic pelvic pain.

Key words: chronic pelvic pain/lofexidine hydrochloride/women

Introduction

The treatment options for women with chronic pelvic pain remain limited. For women without specific pathology identifiable at laparoscopy, interventions demonstrated to be effective in randomized trials are: ovarian suppression with medroxyprogesterone acetate; reassurance with the aid of ultrasound scanning; and a multidisciplinary approach to investigation and treatment (Stones and Mountfield, 1998). Pelvic venous congestion has been identified in women with pelvic pain (Metzger, 1998) both radiologically and using ultrasound scanning (Stones et al., 1990) and the clinical features suggestive of this condition have been described (Beard et al., 1988).

A possible vascular basis for chronic pelvic pain has prompted the evaluation of vasoactive agents for treatment, by analogy with cerebral migraine. Intravenous dihydroergotamine was shown to ameliorate acute exacerbations of pelvic pain (Reginald et al., 1987) but we hypothesized that a sympatholytic drug might reduce pain symptoms by preventing vasoconstriction in the utero-ovarian vascular bed and consequent release of agents with algic and vasodilator properties such as substance P from the vascular endothelium (Stones et al., 1996).

We undertook a placebo-controlled randomized controlled trial of the orally active α₂-adrenoceptor agonist lofexidine hydrochloride, which is licensed in the UK for the treatment of symptoms associated with opiate withdrawal (Cox and Alcorn, 1995) and has previously been evaluated for the alleviation of postmenopausal hot flushes (Jones et al., 1985).

Materials and methods

The study was approved by the local Ethics Committee.

Protocol

Premenopausal women with an intact uterus were eligible for entry into the study if they had had chronic pelvic pain for at least 6 months; laparoscopy had excluded specific causal pathology such as endometriosis, pelvic inflammatory disease or adhesions; they were using effective contraception which was defined as an oral contraceptive pill, barrier methods, intrauterine device or sterilization, and did not have symptoms suggestive of irritable bowel syndrome. A power calculation showed a sample size of 19 in each group to be required to achieve 90% power to detect as significantly different at the 5% level the anticipated response rates of 80% and 30% in the lofexidine and placebo groups respectively. Treatment was for 8 weeks. The protocol included weekly dose increments for the first 3 weeks depending on symptomatic response from an initial dose of 200 μg twice daily to a maximum of 600 μg twice daily. The primary end point was a 50% or greater reduction in the 10 cm visual analogue scale (VAS) for pain at the end of the study. The VAS used was a simple 10 cm line without graduations and the words ‘no pain’ at one end and ‘excruciating pain’ at the other. Additional end points were VAS recorded in a daily diary and the subject’s self-rating of her pain as worse, unchanged, somewhat relieved, considerably relieved or completely relieved.
Table I. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Lofexidine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>29.3</td>
<td>5.2</td>
<td>30.5</td>
</tr>
<tr>
<td>Parity</td>
<td>0.8</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.5</td>
<td>5.2</td>
<td>25.5</td>
</tr>
<tr>
<td>Months of pain</td>
<td>57</td>
<td>67</td>
<td>38</td>
</tr>
<tr>
<td>Initial VAS for pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual</td>
<td>51.2</td>
<td>18.4</td>
<td>59.1</td>
</tr>
<tr>
<td>Most severe</td>
<td>79.1</td>
<td>12.2</td>
<td>84.4</td>
</tr>
</tbody>
</table>

*Parity difference tested by Mann-Whitney U test; others by t-tests.

**Assignment**

Women were randomized using a sealed envelope system to receive lofexidine hydrochloride or placebo.

**Masking**

The randomization code was held independently of the investigators at the office of Britannia Pharmaceuticals Limited and in the hospital pharmacy from which trial medication was dispensed. The investigators were blind to the randomization code until the study was complete. Placebo and active tablets were visually identical and could not be distinguished by taste. Masking was not formally tested at the end of the study.

**Statistical analysis**

Using SPSS (version 10, SPSS Inc.) baseline characteristics of women randomised to the two groups were compared by unpaired t-tests or, for parity, a Mann–Whitney U-test. Pain categories and adverse events were cross tabulated for analysis using χ² tests. The odds ratio (OR) and 95% confidence intervals (CI) for the primary end points were calculated in Review Manager 4 (Cochrane Collaboration, 1999). Daily diary VAS for pain were compared with the end-of-study summary VAS by calculating Pearson’s coefficients.

**Results**

**Participant flow and follow-up**

Nineteen women were randomized to the lofexidine treatment arm and 20 to placebo. Baseline characteristics are shown in Table I: the groups were well matched with regard to age, body mass index (BMI), duration of pain and initial VAS. However, the lofexidine group were more parous (median 2) than the placebo group (P = 0.005). Of those in the lofexidine group nine completed 8 weeks of treatment compared with 14 in the placebo group. Timing and reasons for discontinuation are shown in Table IIa,b.

**Analysis**

Intention-to-treat analysis of those having 50% or more reduction in VAS, where women who discontinued were considered treatment failures, showed improvement in 4/19 of those randomized to lofexidine, and 8/20 of those randomized to placebo (OR for improvement 2.5, 95% CI 0.6 to 10.3). The other end points showed similar lack of efficacy. Use of concomitant analgesia did not differ between the groups: 10/19 of the lofexidine and 8/20 of the placebo group used no analgesia. Four patients in each group reported use of analgesia for pelvic pain during the study period, consisting of paracetamol, non-steroidal anti-inflammatory drugs or combined paracetamol-dihydrocodeine preparations. Five patients in the lofexidine group and eight in the placebo group reported use of analgesics for non-pelvic pain, predominantly headache.

No serious adverse effects were observed. Of the four most common adverse events, drowsiness, dizziness and dry mouth were more common in the lofexidine group, and headache and migraine were more common in the placebo group (Table III).

**Discussion**

This pilot study has not demonstrated the therapeutic efficacy of lofexidine in pelvic pain. The study had adequate power to detect a substantial treatment effect and the present findings indicate that lofexidine will not have a useful role in this
indication, but do not exclude a small treatment effect, potentially detectable with a larger sample size. These negative findings are unlikely to have arisen because of the higher parity of the lofexidine group, and the groups were otherwise well matched. We had hypothesised that reduction of sympathetic outflow would result in a response via the peripheral vasculature. However, recent animal experimental work indicates that \( \alpha_2 \) adrenoceptor agonists have direct antinociceptive effects that are mediated via the \( \alpha_{2A} \) adrenoceptor subtype (Hunter et al., 1997). In an animal model of neuropathic pain the antinociceptive effect of the \( \alpha_2 \) adrenoceptor agonist dexmedetomidine was mediated peripherally rather than via the central nervous system (Poree et al., 1998). In humans, it may be that these agents would show efficacy in chronic pain syndromes more clearly associated with central nervous system sensitization or neuropathy.

A positive finding was the excellent correlation between VAS completed in the daily diary and at the end of the study. This is an important observation for future research in pelvic pain: recollection of previous pain intensity is affected by the stimulus properties (Linton and Melin, 1982) and by present mood (Bryant, 1993) so that accurate recall of the experience of chronic pain cannot be assumed and needs to be demonstrated in individual research settings. In this setting summary measures offered a satisfactory reflection of daily pain experience.

In conclusion, current animal experimental work highlighting the role of \( \alpha_2 \)-adrenoceptors in antinociception may not be directly transferable to humans. Alternatively, it may be that \( \alpha_2 \)-adrenoceptor agonists would show antinociceptive efficacy in human chronic pain syndromes more clearly associated with central sensitisation or neuropathy. Summary VAS for pain are appropriate end-point measures for clinical studies in this group of patients.

References


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