BMC Anesthesiology

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Research article

Ibuprofen 400 mg is effective in women, and women are well represented in trials

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Published: 1 November 2002

BMC Anesthesiology 2002, **2**:6

Received: 31 July 2002
Accepted: 1 November 2002

This article is available from: http://www.biomedcentral.com/1471-2253/2/6

Abstract

Background: A recent article in the New Scientist argued that women were under-represented in clinical trials which, until now, had masked the finding that ibuprofen 400 mg was ineffective in women.

Methods: Meta-analysis of randomised, double-blind placebo-controlled trials of ibuprofen 400 mg in acute pain, and use of individual patient information were planned to test the hypothesis that ibuprofen is ineffective in women. For each trial the proportion of women participating, the number of patients with at least 50% pain relief and the overall event rate for ibuprofen 400 mg and placebo was calculated. For each patient percentage pain relief was calculated, and the numbers of women and men achieving at least 50% pain relief used to calculate number-needed-to-treat (NNT) for ibuprofen 400 mg compared to placebo.

Results: Thirty-seven included trials had 3,577 patients, 67% of whom were women. The proportion with at least 50% pain relief was unaffected by how many women were included. In an analysis of 678 individual patients the proportion of women and men with at least 50% pain relief was the same, NNT 3.4 (2.6 to 4.6) and 2.5 (2.0 to 3.3) respectively.

Conclusion: There is no clinically meaningful difference in the efficacy of ibuprofen 400 mg between men and women experiencing moderate to severe postoperative pain and women were well represented.

Background

One of us (JB) was told by a chiropractor that ibuprofen was ineffective in women, implying that there was little point taking it. This was based on an article in the New Scientist in January 2002 [1] written by a science writer in residence at the Novartis Foundation. A single study of experimental pain in 10 women and 10 men was the source of the assertion that ibuprofen was ineffective in women [2], supported by the claim that this was clinical important: "This is very dramatic, and has a direct impact for the clinic". A further assertion was that women were under-represented in clinical trials of analgesics, which was why

clinical trials had failed to show the ineffectiveness of ibuprofen. The article failed to mention that recent clinical research from the Food and Drug Administration found no gender difference in response rates for ibuprofen in 195 women and 119 men undergoing third molar removal [3].

Our chiropractor was unaware that JB was updating a Cochrane review [4] of ibuprofen in acute pain [5], and that she knew that both assertions were likely to be incorrect based on evidence from over 5,000 patients in clinical comparisons of ibuprofen and placebo. We set out to use the information from the updated systematic review to examine gender differences by analysing clinical trials and individual patient data, and to investigate whether women have been under-represented in clinical trials of ibuprofen.

Methods

Published clinical trials

Search strategy and methods of analysis have been published previously [4,5]. Randomised, double-blind trials were sought that compared ibuprofen and placebo in adult patients with moderate or severe postoperative pain. Trials had to use conventional pain measurement methods from which the outcome of at least 50% pain relief over four to six hours could be obtained [6]. For each trial the proportion of women participating, the number of patients with at least 50% pain relief and the overall event rate for ibuprofen 400 mg and placebo was calculated. Number-needed-to-treat for men and women separately could not be calculated from these trials because they did not report these results by gender.

Individual patient data

Information on 678 individual patients was available from five randomised, controlled trials comparing ibuprofen 400 mg with placebo [7]. All trials used identical criteria and efficacy measures [6] and were assessed using the same techniques as the clinical trials. For each patient percentage pain relief was calculated, and the numbers of women and men achieving at least 50% pain relief used to calculate number-needed-to-treat for ibuprofen 400 mg compared to placebo [8]. The z score was used to determine whether there was a significant difference in the NNT between women and men [9].

Results

Published clinical trials

Forty nine randomised, double-blind comparisons of ibuprofen 400 mg and placebo with 4,703 patients were available. Seven trials were excluded as they failed to provide details of the number of women and men participating within each treatment arm. The five trials with individual patient data were also excluded in order not to duplicate their results within this analysis. That left 37 trials with 3,577 patients, of whom 67% were women (additional file 1). The 37 included studies were of generally high reporting quality (quality scores between 2 and 5, median 4 [10]), known to be associated with minimal reporting bias [11,12].

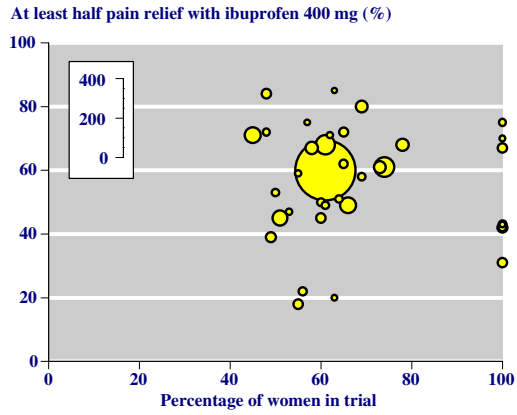

Figure 1
Proportion of patients with at least 50% pain relief with ibuprofen 400 mg according to the percentage of women in the trial. Scatter plot showing the proportion of patients with at least 50% pain relief over 4–6 hours following a single dose of ibuprofen 400 mg in relation to the percentage of women participating in individual published clinical trials included in the meta-analysis.

There were no included trials with fewer than 45% women. Thirty-two of the 37 trials had more than 50% women, and 86% of patients were in trials in which over half the patients were women. Eight trials enrolled only women (647 women), and no trial enrolled only men.

The proportion of patients with at least 50% pain relief from ibuprofen 400 mg (Figure 1) and placebo (Figure 2) was unaffected by the proportion of women included in the trials. The event rates for ibuprofen 400 mg varied between 18% and 85%, a large but expected variation [13]. In the five trials with the lowest proportion (between 45% and 50%) of women the event rate for ibuprofen 400 mg was between 39% and 84%. In the eight trials that included only women the event rate was between 31% and 75%.

Individual patient data

Here, 57% (192/339) of patients treated with ibuprofen 400 mg were women and 63% (214/339) of patients treated with placebo were women (additional file 1).

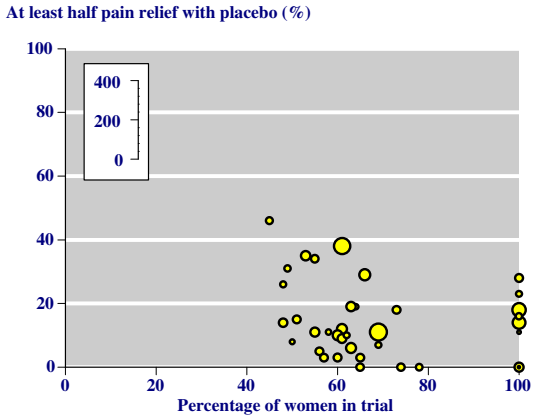

Figure 2
Proportion of patients with at least 50% pain relief with placebo according to the percentage of women in the trial. Scatter plot showing the proportion of patients with at least 50% pain relief over 4–6 hours following a single dose of placebo in relation to the percentage of women participating in individual published clinical trials included in the meta-analysis.

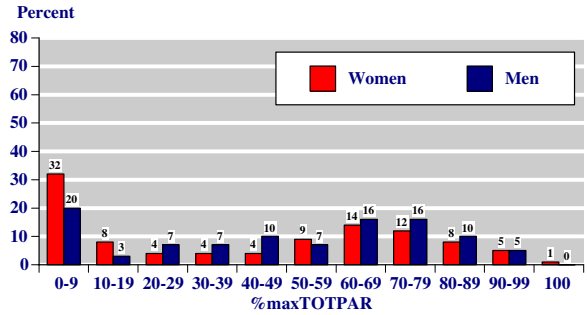

Figure 3
Spectrum of pain relief with ibuprofen 400 mg for women and men. Distribution of pain relief (%maxTOTPAR) experienced by women and men following ibuprofen 400 mg.

The number-needed-to-treat for at least 50% pain relief over four to six hours for women was 3.4 (2.6 to 4.6), not significantly different than that for men of 2.5 (2.0 to 3.3) (z score 1.58, p = 0.11).

The distribution of the percentage of pain relief experienced by individual patients from ibuprofen 400 mg and placebo was the same for both women (192 treated with ibuprofen, 214 with placebo) and men (147 treated with ibuprofen, 125 with placebo) (Figure 3 and Figure 4).

Discussion

We found no evidence that women have been underrepresented in clinical trials of ibuprofen 400 mg because two thirds of all patients were women. There was no difference in the amount of analgesia experienced by women and men following a single dose of ibuprofen 400 mg. If ibuprofen was without effect in women, trials with a larger proportion of women participating would show less effect than those with a smaller proportion. Analysis of 37 trials with 3,577 patients showed no relationship between the proportion of patients with 50% pain relief and the proportion of women included in the trials (Figure 1 and 2). Analysis of individual patient data confirmed this finding, with no significant difference between the NNT for women and the NNT for men or in the overall distribution of pain relief (Figure 3 and Figure 4).

This review includes only 'postoperative' pain trials, a term under which dental, orthopaedic, abdominal, and gynaecological surgery, cesearean section and episiotomy were included. It could be argued that as some of these procedures occur only in women, confounding by procedure and gender would be possible. No evidence of any difference was found for aspirin [14] and a review of primary dysmenorrhoea reported that pain was effectively treated with ibuprofen with an NNT of 2.6 (2.2 to 3.2) [15]. Studies of ibuprofen in arthritis in which the majority of patients were women showed no gender-specific differences in efficacy [16,17].

The important point is the way science is reported, and the disservice that such 'scare' stories can do. A tiny experimental pain study, whose results fly in the face of a wealth of clinical data, was used to score political points about gender. The result of such publicity could be to stop women using an effective therapy for pain. The mass of clinical data here shows that the story was wrong and hopefully will redress the balance. A mexican-wave effect of rumour-based medical reporting will always frustrate the careful collection and application of evidence.

Conclusions

There is no evidence of gender bias in this clinical research or of any clinically meaningful difference in the efficacy of ibuprofen 400 mg between women and men.

Competing Interests

RAM & HJM have consulted for various pharmaceutical companies. RAM, HJM & JE have received lecture fees

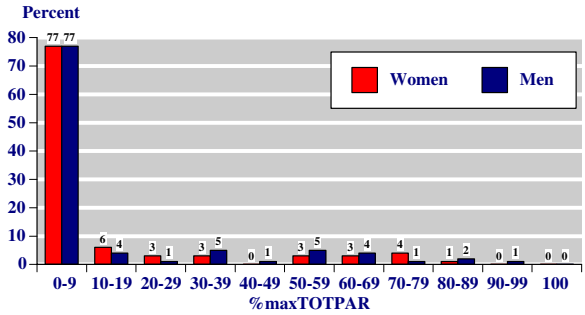

Figure 4
Spectrum of pain relief with placebo for women and men. Distribution of pain relief (%maxTOTPAR) experienced by women and men following placebo.

from pharmaceutical companies related to analgesics and other healthcare interventions. All authors have received research support from charities, government and industry sources at various times, but no such support was received for this work. No author has any direct stock holding in any pharmaceutical company.

Authors' contributions

JB and RAM argued over the importance of this topic, and eventually agreed that it had to be sorted. JB updated the Cochrane review of ibuprofen with supervision and assistance from JE. JB, RAM and JE analysed data. JB and RAM drafted a manuscript, which all authors read, discussed, altered, drafted again, and finally agreed.

Additional material

Additional file 1

Details of included studies
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2253-2-6-S1.pdf]

Acknowledgements

The work was supported by Pain Research Funds, and the Oxford Pain Relief Trust.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

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