

A Search for Sex Differences in Response to Analgesia

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Background: It is generally accepted that males and females respond differently to painful conditions. With few exceptions, according to the published literature, females demonstrate a lower pain threshold and a lower tolerance of painful stimuli. There is some support in the literature that females experience greater analgesic efficacy than do males after the administration of narcotic analgesics. We compared the analgesic response of females and males to ibuprofen in a post-third-molar extraction dental pain model.

Methods: We performed a meta-analysis of 314 subjects included in the ibuprofen treatment arm of 7 double-blind, post-third-molar extraction dental pain (moderate to severe) studies, which were submitted to the agency electronically. The inclusion and exclusion criteria were practically identical in all studies. Pain relief and pain intensity measurements used the same metrics in all studies and were recorded just before and at least at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 hours after drug administration.

Results: The study included 195 female subjects and 119 male subjects (mean age, 21 years). Other than requiring dental extractions, the subjects were all healthy. Post-operative baseline pain was greater in females than in

males to a statistically significant degree ($P = .006$). Both pain intensity and pain relief scores demonstrated the well-established analgesic effect of ibuprofen in the pooled data set as well as in all the individual studies. Moreover, the mean pain intensity and pain relief scores over time for the female and male treatment groups were not noticeably different at any time point after drug administration, with no imputation for missing values. Analysis of the data using the "baseline observation carried-forward" technique for re-medicated subjects (the technique recommended by the Food and Drug Administration for efficacy analysis of acute analgesic medications) produced the same results, which were confirmed by analysis of variance and t tests at each time point of the study.

Conclusions: Our results demonstrated no sex effect on the analgesic response to ibuprofen. These results were obtained under the post-third-molar extraction setting, in which the least possible confounding factors are present. To fully establish the generality of this phenomenon, studies should be carried out in other pain models and using analgesic medications with different mechanisms of action.

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IT SEEMS THAT most experts in the field believe that males and females respond differently to painful conditions.¹⁻¹² Physiological, psychological, and social factors, as well as cellular, molecular, and genetic factors, may all have an impact on the generation and perception of pain. Under experimental pain conditions, using mechanical or thermal stimuli, females demonstrated a lower pain threshold and a lower tolerance of pain.^{1-10,12} Sex differences have also been demonstrated in naturally occurring acute and chronic pain situations.¹³⁻¹⁸ Nevertheless, these sex differences in pain perception are not unequivocal. Some studies have not found a sex-related difference in pain perception

using noxious stimuli,¹⁹⁻²¹ and it has been suggested that there are at present few clear answers on how to apply what we know so far to specific clinical situations.¹¹ Sex differences in analgesic responses have been much less studied. Studies in mice claim to have demonstrated sex and genotype effects on stress-induced analgesia²²⁻²⁵ and sex differences in brain κ -opioid and NMDA receptor activity.²⁶ Very few studies have evaluated sex differences in analgesic response in humans.²⁷⁻²⁹ In these studies, females experienced greater analgesic efficacy than did males after the administration of κ -opioid receptor agonists in the post-third-molar extraction dental pain model in small groups of subjects. There is also

SUBJECTS AND METHODS

We screened all analgesic studies that were recently submitted to the Division of Analgesic, Anti-inflammatory, and Ophthalmic Drug Products, Food and Drug Administration (FDA), that included efficacy data in electronic formats. We selected all analgesic studies in which ibuprofen (400 mg) was the active control. To be eligible for inclusion in our analysis, studies had to be randomized, double-blind trials, including ibuprofen arms using the post-third-molar extraction dental pain model. The databases used contain complete archival records of all subject information from the clinical trials.

The inclusion and exclusion criteria of these trials had to meet certain standard criteria. Eligible subjects had to be otherwise healthy males or nonpregnant females older than 15 years. All subjects selected had to be scheduled to have third molars removed, at least 1 of which was partially embedded in bone and was a mandibular impaction. Subjects must have been experiencing moderate to severe pain after the procedure (>50 mm on a 100-mm visual analog scale). Standard exclusion criteria had to include any analgesic use within 24 hours of the administration of the study medication, recent history of chronic analgesic use, or obesity.

Efficacy end points had to include pain intensity scores measured on a 4-point categorical scale (from 0 [none] to 3 [severe]) and pain relief scores measured on a 5-point categorical scale (from 0 [none] to 4 [complete]). These scores had to be recorded just before and at least at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 hours after drug administration. Rescue analgesic medication was to be allowed, but once a subject received a rescue medication, the time of this event had to be recorded, and the subject was excluded from further pain measurements.

The statistical analysis plan was to combine the raw data of all eligible studies and to analyze the results observed in all randomized patients in the ibuprofen arm. The

data unquestionably demonstrated the efficacy of ibuprofen in lowering pain intensity and in providing pain relief during the 6 hours after the dental extraction. The question to be addressed was whether a comparison over time of the entire set of pain intensity scores and pain relief scores by sex would reveal a systematic difference. Even though the pain scores are recorded as categorical values, experience has shown that the outcome over time is most easily perceived in terms of group averages. Scores grouped by sex were to be averaged and displayed as a function of time for visual inspection. At each recorded time, a statistical analysis program (JMP; SAS Institute Inc, Cary, NC) was used to formally test for the significance of any between-sex differences. The Pearson χ^2 test for categorical data was used. Baseline pain intensity measure had only 2 categories: moderate and severe. We anticipated a larger number of pain intensity score categories at the subsequent post-medication time points (to include none and mild), leading to a smaller count in some cells and potentially casting doubts on the results. For this reason, *t* test values and the findings of nonparametric comparison of pairs were evaluated. The results were consistent in all cases.

The omission from analysis of subjects when they re-medicate gives misleading results about the practical efficacy of different drugs. A drug with many remedicators but with a large amount of pain reduction for nonremedicators can appear superior to a drug with a mixed amount of pain reduction but with few remedicators. To avoid this problem in the comparison of drugs, a standard procedure is to incorporate a penalizing rule as an estimating procedure to account for remedicators. A technique currently in use and recommended by the FDA when remedication occurs is the "baseline observation carried-forward" (BOCF) technique. According to the BOCF technique, remedication is equivalent to no change from the original pain for purposes of analysis. Averaging by sex was also planned and carried out to determine whether sex differences would appear with the BOCF technique.

I report on sex differences in response to cutaneous anesthesia.³⁰

In this study, we evaluated the sex effect in analgesic response among a large number of subjects who were treated with ibuprofen after extraction of the third molar.

RESULTS

Seven studies of post-third-molar extraction dental pain models, with a total of 314 subjects (195 females and 119 males) in their ibuprofen treatment arms, were eligible and included in the analysis. More than 90% of the subjects were white. There were no statistically significant differences in the mean age between females and males ($P=.62$) (**Table**).

The difference in average baseline pain intensity between females and males appears small (Table), a mere 0.16. The difference, however, is attributable to the fact that a larger number of females had severe baseline pain (37% for females vs 27% for males). Initially, there were only 2 pain states: moderate and severe. A categorical analysis was performed, and the results demonstrated that the difference was significant ($P=.006$).

Both pain intensity and pain relief scores demonstrated the well-established analgesic effect of ibuprofen in the pooled data set as well as in all the individual studies. However, the mean pain intensity scores over time for the female and male treatment groups were not noticeably different at any time point after drug administration, with no imputation for missing values (**Figure 1**). Analysis of the data using the BOCF technique for remedicated subjects (the FDA-recommended technique for efficacy analysis of acute analgesic medications) produced the same results (**Figure 2**). Figure 2 shows the SD plotted for each time point. Analysis of the pain intensity scores at each observation time revealed the same lack of sex differences. Applying analysis of variance and *t* tests at each time point confirmed the direct observation. Plotting the pain relief scores over time (**Figure 3**) also demonstrated the lack of a sex effect for this pain measure.

Looking at the results of the individual studies, we found out that 5 of the 7 studies similarly demonstrated no sex differences in mean pain intensity and pain relief scores. Two studies revealed statistically significant sex differences in mean pain intensity scores at 1 through 6

Age and Baseline Pain Characteristics of Female and Male Subjects Treated With Ibuprofen

	Females (n = 195)	Males (n = 119)
Age, y		
Mean \pm SD	21.3 \pm 5.3	21.6 \pm 6.3
Range	15-50*	15-46*
Baseline pain†		
Mean \pm SD	2.38 \pm 0.49	2.22 \pm 0.42
Moderate, No. (%)	122 (63)	92 (77)
Severe, No. (%)	73 (37)	27 (23)

*Leaving out 4 female and 5 male outliers who are older than 35 years, the age range would be 15 to 35 years for both sexes.

†See "Subjects and Methods" section for explanation of scores.

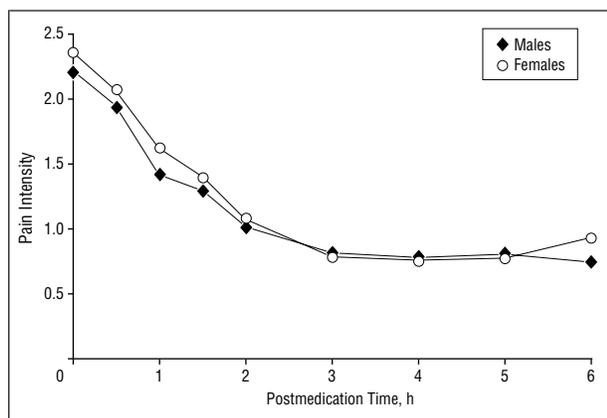


Figure 1. Mean pain intensity scores in female and male subjects over 6 hours after administration of medication (postmedication time).

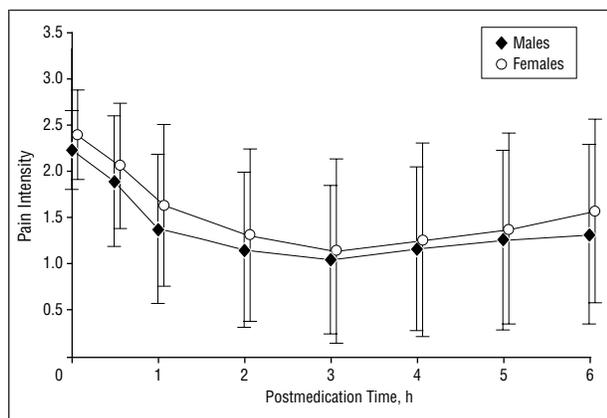


Figure 2. Mean (\pm SD) pain intensity scores in female and male subjects over 6 hours after administration of medication (postmedication time) using the "baseline observation carried-forward" technique.

hours after medication. In one study, however, female subjects had lower pain intensity scores over time after medication, while in the other study, male subjects experienced less pain.

The median time to rescue medication is recommended by the FDA as a primary measure of relief owing to the medication. For the 6-hour data, the median time to rescue medication was 3 hours for both female and male subjects. If the incidence of remediation per-

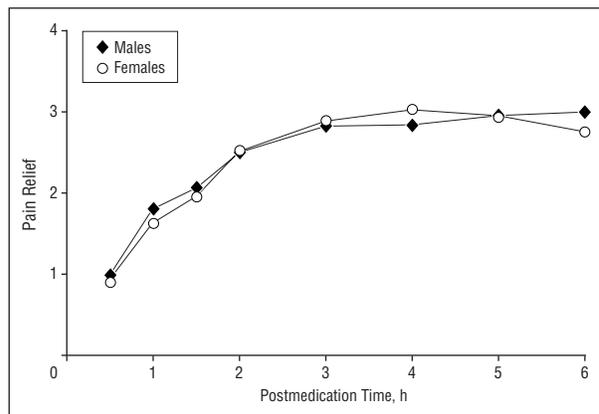


Figure 3. Mean pain relief scores in female and male subjects 6 hours after administration of medication (postmedication time).

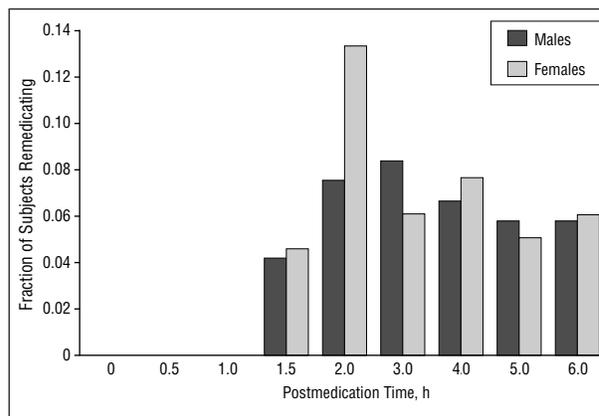


Figure 4. Fractional incidence of remediation in female and male subjects 6 hours after administration of medication (postmedication time).

centages is plotted at each postmedication time point, it appears that more female subjects required rescue analgesia at 2 hours after medication (**Figure 4**). However, on testing, this difference was found not to be statistically significant ($P = .54$). There does not appear to be any systematic sex effect after 2 hours. Furthermore, carrying out a statistical analysis of the data at 2 hours grouped as medicated or unmedicated by sex showed no significant difference with respect to sex ($P = .14$).

COMMENT

In 1993, the FDA took steps to ensure that new drugs would be properly evaluated in women by providing guidance to drug developers.³¹ This guidance emphasized the FDA's expectations that women would be appropriately represented in clinical trials and that new drug applications would include analyses capable of identifying potential differences in drug actions or efficacy between the sexes. However, addressing this issue in the context of individual clinical trials may be difficult because of the large sample size and extensive data collection that may be required in order to stratify and power individual clinical trials. A meta-analytic technique to combine data across like trials is an appropriate way to overcome this obstacle when identical drugs and procedures are used in multiple trials.

Some literature reports have suggested that females may have a lower pain threshold and less tolerance of painful stimuli than males.¹⁻¹² The lower pain threshold of women may be supported by the finding that more females than males reported severe baseline pain in our multitrail study. Also, the larger number of females medicating within the first 2 hours is suggestive of lower pain tolerance. It is possible that this finding reflects sex-based differences in the willingness to report pain thresholds and tolerance of continuing pain. Many individuals will then intuitively predict that if there is a sex difference in response to pain there should also be a sex difference in response to analgesia. Indeed, in an internal survey that we carried out among the FDA reviewers for nonnarcotic analgesic medications (medical officers, pharmacologists, chemists, pharmacokineticists, and statisticians), only 4 of 22 persons predicted no sex effect in response to analgesia. Sex differences in response to narcotic analgesia have been studied in small groups of patients.²⁷⁻²⁹ These studies demonstrated a greater analgesic response to κ -opioids among females and thus led to a hypothesized difference in κ -opioid-activated pain-modulating circuits. In 1 study,³² experimental cutaneous electrical stimulation was used to investigate sex differences in nociception and in response to ibuprofen. The results agreed with those of previous studies in regard to lower pain thresholds and lower tolerance of pain in females. A higher tolerance of the experimental pain after ibuprofen administration (800 mg in a single dose) in males but not in females was also reported. However, the fact that the analgesic effect of 800 mg of ibuprofen was significant in males but nil (not just less) in females raises questions as to the validity of these results. Moreover, the number of subjects included in the study was small (10 females and 10 males), and the study had a preemptive analgesia design (ie, ibuprofen was administered before the noxious stimulus was applied), for which ibuprofen is not indicated.

In our study, no sex differences in analgesic response to ibuprofen were found. It is not possible to determine at this time whether these findings reflect general analgesic response or merely prostaglandin-mediated analgesia.

The post-third-molar extraction pain model may be the best acute analgesia model available at this time. The analgesic effect in this pain model has been reproducibly validated with the use of ibuprofen, other nonsteroidal anti-inflammatory drugs, and other analgesic medications.³³ The post-third-molar extraction pain model is therefore highly recommended by the FDA for the study of analgesic efficacy. Moreover, it is a "clean" model, in the sense that, by nature of the condition, participating subjects are relatively young and without other significant diseases that might be confounding factors in assessing analgesia. Also, subjects who consume other analgesic drugs are excluded from this type of study. Therefore, this dental pain model may be preferable for assessing factors that may potentially affect analgesic response.

At the same time, the difficulty in detecting such an effect arises from the size of the population enrolled in these studies. The FDA usually recommends inclusion of not more than 50 subjects per treatment arm in order

to prevent a small treatment effect from appearing statistically significant. Under these circumstances, if one wants to use the post-third-molar extraction pain model to test the effect of a weaker factor on analgesic response, one has to combine the data from several studies. Although most of the individual trials included in our study demonstrated results in accordance with those of the meta-analysis, the results of 2 of the analyzed trials showed statistically significant sex effects on analgesic response, but in opposite directions. This finding emphasizes the limitation of drawing conclusions in regard to sex-related responses to analgesia based on small analgesia trials.

We performed a meta-analysis in the current study. However, the data from the studies that were aggregated herein are such that our analysis may be regarded as equivalent to that of a multicenter study. The inclusion and exclusion criteria, as well as the full study protocols, were practically the same for all studies. Regardless, most of the concerns usually raised concerning meta-analyses have been addressed. The data collected were the raw data (we did not calculate an average of averages); the measurement tools for collecting end points used in all studies were identical; there was no searching or publication bias; and the quality of all the data met FDA standards.

A potential explanatory factor invoked for possible sex-related differences in response to medications in general is the average lower body weight of females compared with males. Consequently, females may be more highly dosed than males. We did not see a greater analgesic response in the females in our study, suggesting that, at least under these circumstances, the milligram per kilogram of ibuprofen dose did not play a role. Also, to our knowledge, no sex-related difference in the pharmacokinetics of ibuprofen has been described.

There has been speculation that female- and male-related hormones may interact with nociceptive receptors³⁴ and accordingly alter the analgesic response of females throughout the menstrual cycle. No evidence for this speculation is available in the published literature, and we can safely say that in our subject population such an effect would have been averaged out.

CONCLUSIONS

In summary, using the post-third-molar extraction pain model, in which the least possible confounding factors are present, our results demonstrated no sex effect on the analgesic response to ibuprofen. To fully establish the generality of this phenomenon, studies should be carried out with other pain models and using analgesic medications with different mechanisms of action.

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The database used for the preparation of this article was taken from new drug applications of drugs approved by the Food and Drug Administration and is therefore in the public domain through the Freedom of Information Act.

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