Sex-Related Differences in Pharmacological Response to Opioids

Subjects: Pharmacology & Pharmacy

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Clinical experience proves that pharmacological response may vary between the two sexes since pathophysiological dissimilarities between men and women significantly influence the pharmacokinetics and pharmacodynamics of drugs. Opioids seem to produce better analgesia in women especially when they are administered for a prolonged period of time.

Keywords: sex-related differences ; pharmacological response ; adverse drug reactions

1. Introduction

Differences between the two sexes exist, and, from a medical point of view, they have a significant impact on prevalence, incidence, and severity of a wide range of diseases and conditions. Accordingly, physiologic differences between the two sexes affect drug activity with dissimilarities within pharmacokinetics, pharmacodynamics, and pharmacotoxicity. However, most drugs are prescribed to women and men at the same dose, although therapeutic effectiveness varies [1]. In research, women and non-human female mammals have often been underrepresented, especially in previous decades. The reasoning behind it is the assumption that results from males readily apply to females, or the concern that hormonal cycles negatively influence the homogeneity of study populations and complicate experimental designs [2]. Moreover, the risk of ADRs such as teratogenicity or toxicity may outweigh other considerations, and, thus, females of child-bearing potential, pregnant, or breastfeeding are sometimes advised by healthcare professionals against enrolling in such studies [3].

Pharmacokinetics in women is influenced by several factors, such as: lower body weight, higher percentage of body fat, slower gastrointestinal motility, higher gastric pH, decreased intestinal enzymatic activity, and slower glomerular filtration rate [4]. With regard to medication, drugs in women usually have a larger volume of distribution, and the free fraction is also increased. Female sex hormones alter hepatic enzyme activity, which can result in decreased elimination and accumulation for some drugs. However, the way estrogen and progesterone affect pharmacokinetics of drugs is hard to predict and assess, with studies yielding conflicting results [5]. Differences in pharmacodynamics occur when the same plasma concentration of a drug does not cause the same pharmacological response between the sexes. Unlike pharmacokinetic differences, pharmacodynamic disparities are more difficult to assess, as pharmacological effects are not easily measurable [6]. However, there are certain examples in the literature where such differences are obvious. To name a few, women are more likely to experience QT interval prolongation following therapy, while males show a greater sensitivity to propofol's anesthetic effect [7]. Another example would be that verapamil has a lower bioavailability and increased clearance in male patients compared to females [8]. Regarding pharmacotoxicology, women are significantly more likely to be hospitalized secondary to an ADR, as they have a nearly two-fold greater risk than men for exhibiting side effects across many drug classes [9]. For instance, women appear to be at a higher risk for ADRs following treatment with thyroid hormones, phychoanaleptics, and TNF-α inhibitors [10]. Additionally, women are more at risk of admission using thiazide diuretics causing hypokalemia and anticoagulants causing rectal bleeding, whereas males have higher rates of hematuria and subdural hemorrhage following treatment with anticoagulants [11].

2. Opioids

It is well known that pain sensitivity varies among individuals; therefore, assessing and treating postoperative pain requires a personalized approach, making it difficult to follow protocols strictly. An effective analgesia needs to take into account various factors, such as weight, height, age, body mass index, sex, type of surgery, surgery site, preoperative pain, and medication [12]. It is established that the majority of chronic pain syndromes occur more often in women (chronic fatigue syndrome, fibromyalgia, interstitial cystitis, temporomandibular disorder, headache, migraine, low back pain, neck

pain, and osteoarthritis) [13]. Likewise, studies indicate a greater pain prevalence among women and determined that women seem to show greater sensitivity to the majority of experimentally induced pain methods [14][15][16]. However, the differences in pain perception observed within most studies may not be statistically significant and are not always consistent, as suggested by a series of review papers [17][18][19][20]. Pain perception seems to be linked to sex hormones, since testosterone was found to decrease pain sensitivity; thus, a low testosterone state is incriminated in a wide range of chronic pain conditions. Nevertheless, female hormones have both pro- and antinociceptive properties, making the effects of estrogen and progesterone on pain more difficult to evaluate [21]. Regarding opioid addiction, it is established that the desire for opioids is considerably higher among women, and they are at an increased risk of abusing opioids through initial prescription painkiller use [22].

Most pain-related animal studies only include male subjects; few are focused on females, and just a small number are explicitly designed to test for sex differences [23]. Animal studies reveal that, generally, opioid analgesia is more effective in males compared with females. It is known that adult female rodents have a lower percentage of body fat than males, whereas the situation is opposite in humans. These sex-related differences may affect the distribution of highly lipophilic drugs, having a substantial impact on drugs' potency, efficacy, and duration of action [23][24][25]. However, results in human subjects are not as consistent as those in rodents.

Although recent years were marked with significantly increased research regarding sex differences in pain, studies on gender differences in opioids concluded a mixture of different results. Most papers focus on μ agonists, especially morphine, as a main treatment for pain alleviation, since it is perhaps the most clinically significant opioid [26]. Existing data regarding sex differences in response to morphine are highly inconsistent, and a general assumption is difficult to make. It appears that discrepancies in the sex-related response to morphine analgesia might virtually depend on the pain model and/or drug dose/regimen used.

To begin with, some clinical studies investigating the difference in the postoperative morphine requirements determined that male opioid consumption was higher than the one observed in females through patient-controlled analgesia (PCA) [12][27][28]. This means that women self-administer significantly less morphine than men [29]. In addition, further research showed that women experience greater morphine potency, as well as a slower speed of onset and offset of the analgesic effect. However, no sex differences in plasma concentrations of morphine and its major metabolites (morphine-3 and 6-glucuronide) were observed. Those findings suggest that gender differences in opioid analgesia are not related to morphine's pharmacokinetics [25][30]. On the other hand, when analyzing the immediate postoperative analgesia, following intravenous titration of morphine, it appears that women require a higher dosage than men [31][32]. This might be explained by the slower onset of morphine in women, who experience later analgesia. Contrarywise, other research papers reported similar analgesic effects of morphine in both sexes. These studies used experimental pain models and evaluated the response to intramuscular morphine by measuring its plasma levels as well as subjective experience, performance, and physiological effects [33][34]. However, the results on elderly patients appear steadier, with no significant differences in the analgesic effect of morphine being observed in most studies [31][35].

Regarding ADRs, there is considerable, as well as consistent, evidence that sex influences the intensity and frequency of morphine's side effects. Findings indicate that females have a substantially higher risk of developing nausea and vomiting than men following opioid analgesia [36]. These observations might be related to the higher frequency of post-operative nausea and vomiting among women than men [37][38]. However, the same results were also obtained in a study of narcotic-induced emesis in the emergency department, which strengthens the initial conjecture [39]. Furthermore, additional studies reported greater morphine-induced respiratory depression in females than in males [40][41] as well as an increased feeling of disorientation and sluggishness [42]. In addition, preliminary results suggest some cardiovascular differences between the two sexes following IV morphine administration: women experienced a lower heart rate, but only men developed hypertension and had an attenuated cardiovascular response to ischemic pain. However, the observed differences were small, and only one low morphine dose was tested; therefore, further investigations are needed [34].

Leaving morphine aside and analyzing opioids as a whole, the same conclusion can be drawn—distinct investigations reveal various results. It appears that earlier studies tend to deduce that opioids are better analgesics for females [43][44][45]. However, it is hypothesized that this may happen because older studies did not correct for the body weight differences between the two sexes [46]. For instance, the mixed μ-k-opioid agonist-antagonist nalbuphine, butorphanol, and pentazocine produced significantly better postoperative analgesia in women than in men [47]. In contrast, other studies using experimental pain models showed that pentazocine produced analgesia of similar magnitude in men and women [48][49]. Regarding μ-opioids, a similar analgesic response in the two sexes is achieved after the administration of alfentanil, as well as morphine's active metabolite, morphine-6-glucuronide [50][51]. Considering PCA studies on μ-opioids, it generally appears that opioid consumption is higher in men than in women. However, most studies actually assess opioid

consumption rather than pain relief. Therefore, PCA poses problems in terms of reliability, as it can be influenced by other factors than just postoperative pain, such as: expectations, baseline pain sensitivity, fear of addiction, and the occurrence of unpleasant ARDs, such as nausea and vomiting [52].

The general verdict regarding the diverse outcomes of studies is that results may be influenced by procedural and subject variables. Broadly, opioids seem to produce better analgesia in women, especially when they are administered for a few days, as the onset of action is delayed in this category of patients. However, the various responses to pharmacological pain interventions appear inconsistent and dependent on treatment type, genotype, gonadal steroid hormone state of subjects, and characteristics of the pain and the provider [14][16][26][53].

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