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UPCOMING ISSUES

What Does Pain Hurt?

Pelvic Pain

Opioid Abuse Risk

Gender Differences in Responses to Medication and Side Effects of Medication

In recent years, there has been growing interest and increasing recognition that sex and gender may play a significant role in a person's response to medication and should be an important part of individual prescribing. The reasons for sex differences in medication response are clearly multifactorial, encompassing a wide range of aspects from the effects of sex steroid hormones and organ physiology to psychological and sociocultural factors. It is becoming clear from human and animal studies that a number of endogenous neuroactive substances and receptors are influenced by hormonal manipulation, and that drugs routinely given for analgesia, for example, act upon these chemicals or receptors, as shown in Table I.¹ Genetic factors may also play a part; for example, sex-specific differences have been found within the cytochrome p450 superfamily of enzymes involved in the metabolism of both therapeutic medications and endogenous compounds, including sex steroid hormones.² Sex and gender differences are now being reported in the side effects of individual drugs.³

Psychological and Sociocultural Differences between the Sexes

The term "sex" refers to biological differences as a result of chromosomal complement, whereas "gender" is defined by self-representation and social response.⁴ Sexual dimorphism begins in fetal life, continues during childhood and adolescence, and in turn becomes influenced by gender roles. Sex and gender differences are interactive and should not be attributed solely to sex hormones, because dissimilar environmental exposures and experiences will lead to differences in health and illness between individuals as well as therapeutic outcomes. Thus, expected responses to medication, as determined by controlled clinical trials, may in practice be affected by gender role expectations, lifestyle, and cultural differences.⁵ One population study has shown that women are more likely than men

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to seek health care and that they use more analgesic medications, potentially increasing the risk of unwanted side effects and dependency.⁶

Women in Drug Trials

Drug trials and laboratory and clinical research in pain have largely been conducted in males in the past, leading to a relative paucity of information on differences between males and females in terms of drug toxicity, side effects, and differences in pharmacokinetics and pharmacodynamics.⁷ In particular, few studies have been designed to examine sex-specific issues such as the effect of hormone interactions on pharmacological action and the effects of the menstrual cycle. Some studies involve small numbers of subjects without sufficient power to detect statistically significant differences, and results have been conflicting. Animal studies may not prove to be the best models, as pharmacokinetic and pharmacodynamic differences are known to exist between species.

The importance of sex and gender differences in pain and analgesia has recently been recognized by a consensus report from the Special Interest Group on Sex, Gender, and Pain of the International Society for the Study of Pain (IASP) with the recommendation that sufficient numbers of both men and women should be included in drug trials in order to detect the effects of sex or gender.⁸

Adverse Drug Reports in Women

Sex or gender may be a significant risk factor for the development of adverse drug reactions. Side effects and complications of medication are more prevalent in women than men, with one review article noting an almost twofold increase in adverse drug reactions in women compared to men.⁹ Women also report more adverse effects to perioperative analgesic drugs.³ Mechanisms for these adverse effects are likely to include pharmacological differences in drug handling and response in addition to immunological and hormonal factors. Furthermore, multiple drug use may be more common in women, leading to an increased propensity for unwanted drug

interactions and problems with treatment adherence. In particular, exogenous hormones such as hormonal contraceptives may have significant pharmacokinetic interactions with other medications.

Physiological Differences between the Sexes

Differences in organ physiology and body structure between men and women affect drug pharmacodynamics and pharmacokinetics and can potentially alter the drug's efficacy and the likelihood of side effects. This section describes some confounding factors influencing clinical studies.

The cardiovascular system is in part under the influence of the hormonal system, and blood pressure is generally lower in women than men. Studies have shown that blood pressure is inversely related to pain sensitivity, with significant sex differences in pain threshold and tolerance.¹⁰ Thus, baseline measures may differ between sexes and affect pharmacological results.

Women have greater minute ventilation and lower tidal volumes than men, possibly due to the effects of progesterone as a ventilatory stimulant.¹¹ This difference may affect respiratory side effects as well as drug absorption via the respiratory tract, which will vary with respiratory rate and depth.

Exogenous hormones such as hormonal contraceptives may have significant pharmacokinetic interactions with other medications

Sex Differences in Pharmacokinetics

Pharmacokinetic variability between the sexes is thought to arise from a number of factors, including body composition, gastric emptying time, enzyme activity, and drug clearance.

Bioavailability

A drug's bioavailability will depend on its physical properties and formulation as well as on the route of administration and physiological factors. For oral drugs, some elements are still

debated, such as the role of sex hormones on the gastrointestinal tract (although progesterone can reduce gastrointestinal motility¹²), as well as the vulnerability of some women to alcohol-related disease due to reduced gastric oxidation of ethanol.¹³ In women the absorption of aspirin may be decreased, possibly due to lower activity of aspirin esterase.¹⁴

As our understanding of sex and gender effects in pharmacokinetics and pharmacodynamics increases, we may start to apply this knowledge in our routine practice

Examples of clinically available drugs that act on neurochemicals or receptors influenced by hormones

Drugs	Neurochemicals/Receptors
Anticonvulsants	Gamma-aminobutyric acid (GABA)
Antidepressants	Serotonin/5-hydroxytryptamine (5-HT)
Clonidine	Angiotensin
Cortisol	Corticotropin-releasing hormone Adrenocorticotrophic hormone
Ketamine	N-methyl-D-aspartate (NMDA) Glutamate
Opioids	Enkephalins Pre-proenkephalin
Somatostatin analogues	Somatostatin
Tetrahydrocannabinol	Cannabinoids

Table 1

Distribution

Drug distribution depends on body composition. Women may have more varied responses because of (1) a higher body fat content, which may alter the volume of distribution for lipophilic drugs such as benzodiazepines and alcohol; and (2) changes in water and electrolyte balance during the menstrual cycle that can potentially alter plasma drug concentrations. It is important to remember that models for body composition must also be adjusted for age and body size, because total body water decreases with age.

Sex differences in drug binding may affect free drug concentrations and carry a potential for toxic effects, especially for drugs with a narrow therapeutic index. In particular, sex steroid hormones may alter protein binding and increase free drug concentration of amide local anesthetic drugs. Progesterone and estradiol both affect the pharmacokinetics of bupivacaine and lidocaine.¹⁵ Studies have shown that women have significantly lower concentrations of α -1 acid glycoprotein, a major binding protein for neutral and basic drugs.¹⁶ Pharmacokinetic studies in pregnant women have observed reduced drug binding and increased concentrations of free drug in plasma due to the reduction in plasma albumin concentration from relative hemodilution.¹⁷ Sex differences have also been found in the levels of the drug transporter p-glycoprotein, with lower hepatic levels in women causing significantly increased levels of substrate drugs such as vincristine and doxorubicin.¹⁸

Metabolism

Significant discrepancies have been demonstrated between the sexes in terms of drug metabolism, with individual cytochrome p450 isoenzymes being implicated. Studies of drugs that undergo CYP3A metabolism in the gastrointestinal tract and liver have found sex differences in the oxidative metabolism of a number of substrates. One study investigating midazolam metabolism showed that women had higher CYP3A activity than men, and that these differences could be explained by hormonal changes occurring during the menstrual cycle.¹⁹ These findings imply that women

may eliminate other drugs, including sex steroid hormones, more rapidly by the same mechanism.

Excretion

Creatinine clearance, a surrogate marker of glomerular filtration rate and hence of drug excretion via the kidneys, is generally higher in men than women due to men's increased muscle mass and larger size. Although clearance has been shown to vary with the menstrual cycle, the clinical implications are unclear. One review paper concluded that sex differences in the renal clearance of drugs are generally of minor importance.²⁰

One population study has shown that women are more likely than men to seek health care and that they use more analgesic medications, potentially increasing the risk of unwanted side effects and dependency

Sex Differences in Pharmacodynamics

Sex differences in pharmacodynamics have been observed in a number of drugs; some specific examples relating to analgesic drugs are discussed below.

Opioids

Women generally have more adverse effects (e.g., nausea and vomiting) than men after opioid administration.²¹ Sex differences have been observed in morphine-induced depression of respiration, with one study showing that young women had a decreased ventilatory response to carbon dioxide and hypoxia compared to men following an analgesic dose of morphine.²² Short- and longer-term effects of opioids may show differences between the sexes, as evidenced in the immediate postoperative period, when women are seen to have a greater requirement for opioids,²³ whereas men have higher opioid consumption later, after the initial recovery period. This difference may be partly explained by the faster recovery after general anesthesia in women²⁴ and by the fact that

women are more likely to adopt a multidisciplinary approach to pain management. Another study reported increased postoperative morphine usage in Chinese men after the recovery period in the first three days postsurgery and greater movement-induced pain on the second day postsurgery.²⁵

Responses to partial kappa-opioid agonists such as nalbuphine, butorphanol, and pentazocine have shown greater analgesia in women, whereas men who were given nalbuphine experienced an anti-analgesic effect that was reversed by low-dose morphine.²⁶ More recently it has been postulated that kappa-opioids may exert their analgesic action specifically on women with more than two variant melanocortin receptor 1 alleles.²⁷ However, the findings from experimental pain assays, in contrast to the postoperative pain models, show no significant sex differences in pentazocine²⁸ or butorphanol²⁹ analgesia.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Acetaminophen (Paracetamol)

Significant sex differences in acetaminophen metabolism were observed in one study, with increased sulfate conjugation and reduced glucuronide conjugation in Caucasian women compared with men.³⁰ For ibuprofen, a small laboratory study that demonstrated that men had a greater analgesic effect from ibuprofen than women generated a review of clinical data.³¹ The subsequent meta-analysis found no difference between men and women in the efficacy of ibuprofen for moderate to severe postoperative pain.³² However, researchers are now focusing on sex differences in NSAID adverse effects and age-related outcomes.

Few studies have been designed to examine sex-specific issues such as the effect of hormone interactions on pharmacological action and the effects of the menstrual cycle

Conclusion

Sex and gender differences are present in both therapeutic responses to medication and adverse

effects, with significant implications not only for health but also for health economics. The high prevalence of adverse drug reactions in women may in part reflect the pre-licensing clinical trials carried out mainly in men in the past. The importance of sex differences is being realized in drug development, prescription, and dosing, with the National Institutes of Health Revitalization Act of 1993 requiring that women be included in all phases of clinical trials. One review article, however, still found women to be underrepresented in many federally funded clinical trials, including studies of interventions for diseases that affect both men and women.³³ The inclusion of pregnant and postpartum women, as well as women of childbearing age, continues to raise safety, legal, and ethical issues.

In future, we envisage individualized treatment and medication strategies, with the inclusion of sex and gender as well as physiological and pharmacological variables being the accepted standard

Knowledge evolving from clinical trials and from the study of sex and gender differences can potentially lead to different doses or dosing intervals between men and women, or even the use of different drugs to achieve the same purpose. As our understanding of sex and gender effects in pharmacokinetics and pharmacodynamics increases, we may start to apply this knowledge in our routine practice. An example is the use of target-controlled infusions in anesthetic practice. More recent pharmacokinetic models for propofol and remifentanyl now include sex-specific data, with the patient's weight, height, age, and sex to be entered into the delivery system program. In future, we envisage individualized treatment and medication strategies, with the inclusion of sex and gender as well as physiological and pharmacological variables being the accepted standard.



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