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Review Article

Gender differences in drug effects: implications for anesthesiologists

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Background: The gender aspect in pharmacokinetics and pharmacodynamics of anesthetics has attracted little attention. Knowledge of previous work is required to decide if gender-based differences in clinical practice is justified, and to determine the need for research.
Methods: Basis for this paper was obtained by Medline searches using the key words 'human' and 'gender' or 'sex,' combined with individual drug names. The reference lists of these papers were further checked for other relevant studies.
Results: Females have 20–30% greater sensitivity to the muscle relaxant effects of vecuronium, pancuronium and rocuronium. When rapid onset of or short duration of action is very important, gender-modified dosing may be considered. Males are more sensitive than females to propofol. It may therefore be necessary to decrease the propofol dose by 30–40% in males compared with females in order to achieve similar recovery times. Females are more sensitive than males to opioid receptor agonists, as shown for morphine as well as for a number of kappa (OP_2) receptor agonists. On this basis, males will be expected to require 30–40% higher doses of opioid analgesics than females to achieve similar pain relief. On the other hand, females may experience respiratory depression and other adverse effects more easily if they are given the same doses as males.
Conclusion: These examples illustrate that gender should be taken into account as a factor that may be predictive for the dosage of several anesthetic drugs. Moreover, there is an obvious need for more research in this area in order to further optimize drug treatment in anesthesia.

Key words: Adrenergic agonists; adrenergic beta-antagonists; analgesics, benzodiazepines; cytochrome P-450, gender; human; neuromuscular blocking agents; non-narcotic analygesics; opioid anesthetics; sex.

'*THERE are two major classes of living organisms – male and female. In many cases, they are so different in form and habit that one might well be excused the thought that males and females are different species*' (1).

In recent years it has become clear that gender differences exist both in the pharmacokinetics and the pharmacodynamics of drugs related to the practice of anesthesia. Some of these differences are of clinical importance whereas others are mainly of theoretical interest. Differences in pharmacokinetics are more straightforward to study than differences in clinical effects because it is a relatively simple procedure to measure drug concentrations in human plasma. Therefore, more data are available on differences in pharmacokinetics than on differences in pharmacodynamics or clinical outcome. However, isolated pharmacokinetic data are of less value if they are not accompanied by measurements of clinical effects or outcomes.

The aim of this paper was to present an overview of gender differences in the pharmacokinetics and pharmacodynamics of drugs used in the practice of anesthesia, and to discuss whether these differences are of clinical significance. Gender differences in physiological parameters are beyond the scope of this article and will only be briefly discussed. The basis for this paper was obtained by Medline searches using the key words 'human' and 'gender' or 'sex', combined with individual drug names. The reference lists of these papers were further checked for other relevant studies. No information on gender differences was identified for anticholinergic agents. Finally, we also searched for relevant review articles, which are listed in Table 1.

In the first part of this review, general aspects related to gender differences in the pharmacokinetics and pharmacodynamics of drugs are presented. In the second part, individual studies on gender differences

Table 1

Some literature reviews on the impact of gender in clinical pharmacology and therapeutics.

Author(s) (year)	Title	Comment	References
Wilson (1984)	Sex-related differences in drug disposition in man	General review on gender effects in pharmacokinetics	118
Teichmann (1990)	Influence of oral contraceptives on drug therapy	General review on use of oral contraceptives on pharmacokinetics	119
Harris et al. (1995)	Gender effects in pharmacokinetics and pharmacodynamics	General review on gender effects	13
Kando et al. (1995)	Gender as risk factor for adverse events	General review on gender effects focusing on adverse drug reactions	120
Pollock (1997)	Gender differences in psychotropic drug metabolism	Review on gender effects for psychotropic drugs, including benzodiazepines	121
Xie et al. (1997)	Gender-related considerations in clinical pharmacology and therapeutics	General review on gender effects	122
Vinge (1998)	Men and women respond differently to drugs	General review on gender effects (in Swedish)	123
Ciccone et al. (1999)	Drugs and sex differences: a review of drugs relating to anaesthesia	Review on gender effects for anesthetic drugs	124
Beierle et al. (1999)	Gender differences in pharmacokinetics and pharmacodynamics	General review on gender effects	125
Miaskowski and Levine (1999)	Does opioid analgesics show a gender preference for females	Review of 18 published studies in which females and males were compared	126
Kest et al. (2000)	Gender differences in opioid-mediated analgesia	Review including animal and human studies	127
Meibohm et al. (2000)	Gender differences in opioid-mediated analgesia	Gender review on gender effects in pharmacokinetics	115

are reviewed and clinical implications discussed. A summary of drugs for which gender seems to be of clinical significance is presented in Table 2. Drugs for which there are pharmacokinetic differences but where the clinical significance is unknown are summarized in Table 3. Drugs for which there are both pharmacodynamic and pharmacokinetic gender differences and where the differences may tend to cancel each other are listed in Table 4. When not specifically stated, patients studied were ASA class I or II. When only the total number of subjects in a study is stated, the study has included equal numbers of females and males.

Gender differences in pharmacokinetics

Drug distribution

Females and males have different body compositions. The body fat percentage is larger and the body water content is smaller in females. Furthermore, these

Table 2

Anesthetic and related drugs for which the clinical effects may be different in males and females.

Drug	Outcome in females	Mechanism	Level of documentation
Propofol	Decreased effect	Presumably mainly pharmacodynamic	Shown in several clinical studies (41, 43, 45, 46)
Morphine	Increased effect	Most likely pharmacodynamic	Shown in two studies in healthy volunteers (19, 54) and several studies in patients (50–53, 57)
κ (OP_2) receptor opioids (pentazocin, nalbuphine, butorphanol)	Increased effect	Unknown (pharmacodynamic?)	Shown after oral surgery in three small studies (23, 24, 65)
Rocuronium	Increased effect	Lower volume of distribution in females	Shown in one clinical study (84)
Vecuronium	Increased effect	Lower volume of distribution in females	Consistently shown in clinical studies (75–77)
Pancuronium	Increased effect	Lower volume of distribution in females	Shown in one clinical study (79)
Tirilazad	Ineffective when given in the same doses as to males	Higher clearance in females (CYP3A4-related?)	Consistently shown in several clinical trials (9, 108–111, 115)

Table 3

Anesthetic and related drugs for which pharmacokinetics is different in males and females, but where it is unknown whether there are any gender differences in clinical effect.

Drug	Outcome in females	Mechanism	Level of documentation
Alfentanil	Decreased plasma concentration	Higher clearance in females (CYP3A4-related?)	Shown in two small studies (11, 12)
Oxazepam	Increased plasma concentration	Lower clearance in females (glucuronidation)	Shown in one study in healthy volunteers (70)
Paracetamol	Increased plasma concentration	Lower clearance in females (glucuronidation?)	Shown in two studies in healthy volunteers (98, 99)

differences are age-dependent, with body fat increasing in both genders with age. Body fat composition may affect the volume of distribution of many drugs. For lipophilic drugs such as opioids and benzodiazepines, the volume of distribution per kg body weight generally will be higher in females than in males. Conversely, the volume of distribution for water-soluble drugs such as muscle relaxants may be lower in females than in males. Thus, the same dose per kg body weight will result in a lower initial plasma concentration of lipophilic drugs in females, whereas the initial concentration of water-soluble drugs will be higher. As the central volume of distribution is the most important pharmacokinetic factor determining the initial drug concentration after single-dose administration, these gender differences may have an impact on the optimal dosage when the drug is given as one or a few single doses. In contrast, the volume of distribution has no direct influence on the drug concentration at steady state.

Volume of distribution for a drug is defined as the ratio of the plasma concentration and the amount of drug in the body. The practical use of this concept is that it determines the amount of drug that has to be given to reach an initial target concentration. For many drugs, a bolus dose is given to achieve the immediate target concentration. As most anesthetic drugs have several pharmacokinetic compartments, it is not possible to reach steady state immediately, but to maintain a steady (target) concentration in the central compartment. This is achieved by giving a bolus dose corresponding to the volume of distribution of the central compartment, and then start an infusion that compensates for redistribution from the central to the peripheral compartments and elimination from the central compartment over time. This loss will be reduced with the duration of the infusion, as the concentrations in the peripheral compartments increase.

On average, females have lower body weight than males. Thus, when interpreting published studies, it is important to check whether the dose was given on a mg kg^{-1} basis or as the same total dose to all subjects irrespective of body weight. In the latter case, the mean body weight should ideally be the same in females and in males in order to justify direct comparisons of initial drug concentrations.

Drug elimination

Although drugs are commonly compared in terms of elimination half-lives, clearance is (in addition to the dose and bioavailability of the drug) the principal parameter that determines the concentration of a drug at steady-state conditions.

Clearance of a drug is defined as the volume of plasma that is completely cleared for the drug per

Table 4

Anesthetic and related drugs for which there are both pharmacokinetic and pharmacodynamic gender differences.

Drug	Pharmacokinetic effect in females	Pharmacodynamic effect in females	Net effect	Reference
Diazepam	Reduced initial concentration due to higher volume of distribution; possibly higher clearance	Possibly increased sensitivity	Unknown; presumably close to equal?	67, 69, 72
Metoprolol	Lower clearance	Same or decreased sensitivity? (data are inconsistent and partly based upon studies with beta-receptor stimulating agents)	Increased effect in females; alternatively no difference	91, 92, 94, 95
Methylprednisolone (and other glucocorticoids?)	Higher clearance (CYP3A4-related?)	Increased sensitivity	Unknown; presumably close to equal?	107

time unit, usually expressed in $ml\,min^{-1}$ or $l\,h^{-1}$, or alternatively also related to body weight. This is a very useful parameter in anesthesiology because it determines the infusion rate needed (at steady state) to maintain a steady (target) concentration of the anesthetic drug.

For most intravenous anesthetic drugs, hepatic metabolism is the major route of elimination, indicating the significance of liver clearance in anesthesia. Because of a lower cardiac output, females generally have a reduced total liver blood flow compared with males. Consequently, females may also have a possibly lower clearance. However, for low-extraction drugs metabolized by the hepatic cytochrome P-450 (CYP) system, gender differences in enzyme activity are more important than differences in liver blood flow. Although there are more than 50 hepatic CYPs, seven individual CYPs, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 (including the polymorphic CYP3A5) are the most central. For several of these enzymes, gender differences in metabolic activity have been demonstrated or suggested (Table 5). The anesthetic drugs known to be metabolized by these enzymes are listed in Table 6.

Another component of gender-related differences in drug disposition is the use of contraceptive pills, pregnancy, menstrual cycle and menopause, and the associated effects of hormonal changes. The use of contraceptive pills may modify CYP enzyme activities (Table 5). Pregnancy may also increase the activity of hepatic enzymes, particularly CYP2D6 (2). Some evidence indicates that the clearance of drugs in general may be higher on day 15 than on day one in the menstrual cycle in females not taking oral contraceptives (3). However, for anesthetic drugs, no such differences have been revealed. There was no influence of the menstrual cycle on the disposition or systemic clearance of alfentanil (4). Similarly, the clearance of alprazolam was not different between the follicular and luteal phases (5, 6). When the clearance of i.v. midazolam was evaluated in 10 young females during their menstrual cycle, minimal intraindividual variability was found (7). There were no differences in eltanolone pharmacokinetic parameters measured during the follicular and luteal phases (8).

Very limited information is available regarding the menopause and the disposition of anesthetic drugs. Midazolam clearance was lower in postmenopausal compared with premenopausal females (0.64 ± 0.12 vs. $0.47 \pm 0.11\,l\,kg^{-1}\,h^{-1}$), however, there was no effect of estrogen or estrogen plus progesterone replacement therapy in the postmenopausal females on midazolam clearance (9). Another investigation found no difference for any kinetic parameter between young and elderly females, and observed no effect of replacement therapy (10). However, for alfentanil it has been demonstrated that clearance decreases with age (11) in females (12); a decline that has been attributed to a difference between the premenopausal and postmenopausal states (see the section 'Alfentanil'). Prednisolone clearance was lower in postmenopausal compared with premenopausal females, however, there was no effect of supplemental hormone administration on prednisolone clearance (13). In contrast, for the disposition of other CYP3A4 substrates, no effect of menopause has been shown (13, 14).

The conjugation of drugs also seems to be gender dependent (Table 5). For example, the glucuronidation

Table 5

Hepatic cytochrome P-450 and UDP-glucuronosyltransferase activity according to gender and use of oral contraceptives. In females (middle column), the arrows indicate enzyme activity compared with males. For the use of oral contraceptives (right column), the arrows indicate enzyme activity compared to females not using contraceptive pills.

Enzyme	Females	Use of oral contraceptives
CYP1A2	↓	↓
CYP2C9	0*	0*
CYP2C19	↑/↓†	↓
CYP2D6	↑/0†	↓*
CYP2E1	↑/↓†	↑
CYP3A4	↑‡	↓/0†
UGT§	↓*	↑¶

↑, enzyme activity increased; ↓, enzyme activity decreased; O no difference.
*Data are inconsistent or scarce, but most evidence suggest that the given relationship may exist. If any effect is present, it seems to be weak.
†Results are contradictory: Results from published studies may vary depending on the methodology employed, including the substrate used for testing and the ethnicity of the population studied.
‡Might be confounded by a lower activity of P-glycoprotein in females.
§Several isoforms exist; these are not well characterized regarding drug specificity.
¶At least for some isoforms, use of oral contraceptives increase the enzyme activity to an even higher activity than the activity in males.
CYP, cytochrome P-450; UGT, UDP-glucuronosyltransferase.

Table 6

Hepatic cytochrome P-450 (CYP) enzymes involved in the metabolism of drugs used in anesthesia.

Group	CYP1A2	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4
General anesthetics	–	Propofol*	Propofol*	Hexobarbital	–	Halothane Enflurane Isoflurane Sevoflurane	–
Analgesics	–	–	–	–	Codeine Tramadol Oxycodone Hydrocodone	–	Fentanyl Alfentanil Sufentanil* Methadone Buprenorphine
Local anesthesics	Ropivacaine	–	–	–	–	–	Lidocaine Ropivacaine Bupivacaine
Benzodiazepines	–	–	–	Diazepam	–	–	Midazolam Diazepam*
Adjuvants	Theophylline	–	NSAIDs†	Propranolol	Metoprolol Propranolol	–	Verapamil Tirilazad Glucocorticoide

*Studied in vitro.
†Non-steroid anti-inflammatory drugs.

of oxazepam, paracetamol and diflunisal appears to be higher in males than in females. In contrast, no differences were found for the i.v. steroid eltanolone, which is also eliminated by glucuronidation. No information is available on the glucuronidation of other drugs of major importance, such as morphine. Apparent inconsistencies in this field may be caused by the fact that different isoenzymes, which are not fully characterized, are involved in the glucuronidation of various drugs.

The glomerular filtration rate, which is the most important renal parameter for the excretion of drugs that are not actively secreted or reabsorbed, is lower in females than in males. However, this is most probably a consequence of differences in body weight rather than a true gender effect. The effect of gender on tubular secretion and reabsorption is not well characterized and the results are inconclusive.

Traditionally, the interrelationship between the volume of distribution and clearance in steady state has been described by means of the elimination half-life. Terminal elimination half-life for a drug is the time it will take to reach a 50% reduction of its concentration in plasma after drug absorption and distribution are terminated. This reduction results from drug elimination (metabolism and excretion) from the body.

However, terminal elimination half-life is not a very useful parameter in anesthesia as most anesthetics are described by multiple compartments and termination of the effects are usually not only dependent on systemic elimination, but to a larger extent on the (re-) distribution of the drug from the central compartment (brain, blood, heart, kidney) to deeper compartments such as muscle and adipose tissue. Thus, the elimination half-life can not be used to determine the time it will take to reach a 50% decrease in the plasma concentration of an anesthetic agent. The longer the duration of an infusion, the more drug in the tissues, and the longer it will take to reach the 50% reduction after discontinuation of the infusion. Therefore, the term context-sensitive half-life is more suitable in anesthesia (15). Context-sensitive half-life for a drug is the time it will take to reduce the concentration of the drug in plasma to 50% as a function of the duration of an infusion.

For drugs with large volumes of distribution, such as thiopental, context-sensitive half-lives will increase considerably with the duration of the infusion. In contrast, drugs with small volumes of distribution, such as remifentanil, will display relatively constant context-sensitive half-life regardless of duration of infusion. Little is known about the gender aspects of context-sensitive half-life. However, in a study comparing the pharmacokinetics of the steroid anesthetic eltanolone in female and male patients, context-sensitive modeling indicated that it might take females 10 min more than males to recover from an eltanolone infusion of 2-h duration, because of the two-fold greater volume of distribution at steady state in females (16).

Drug concentration at the effect site

The final pharmacokinetic parameter to be discussed is the effect-site equilibration time. This parameter

actually links pharmacokinetics to pharmacodynamics. Effect-site equilibration time is the temporal dissociation between the serum (central compartment) concentration and the apparent effect site (effect compartment) concentration of a drug. This kinetic-dynamic dissociation can be quantified by a rate constant, k_{e0}.

The effect-site equilibration time can be determined by measuring serum concentrations and a pharmacodynamic outcome simultaneously. For a drug like thiopental, the dynamic outcome may be time to loss of a syringe or EEG burst suppression (17, 18). Drugs with a high k_{e0} such as thiopental have a rapid equilibration, while drugs with a low k_{e0} have slower equilibration. Little is known about gender differences of effect-site equilibration time, but a recent study on morphine indicates that gender may also play a role in this context (19).

Gender differences in pharmacodynamics

Less is known about gender differences in drug pharmacodynamics than in pharmacokinetics. Some evidence exists to suggest that it may be gender differences in the expression of adrenergic receptors that may have consequences in the treatment with adrenergic agonists and antagonists. However, the clinical importance of these possible differences is unclear (see the section 'Cardiovascular drugs').

Both experimental and clinical data indicate that gender differences may be of clinical significance in pain physiology. Experimental studies have shown that males tolerate higher levels of pain stimulation than females (20, 21) and that females have a significantly higher μ (OP_3) receptor binding potential than males (22). Moreover, κ (OP_2) receptor agonists such as pentazocine, butorphanol and nalbuphine produce stronger analgesia in females than in males (23, 24). It has also been shown that females are more sensitive to the analgesic effects of morphine than males (19, see the section 'Opioid analgesics').

Inhalational anesthetics

Studies comparing gender or including gender in the analysis of effects were identified for most currently approved inhalational anesthetics except enflurane.

Halothane and isoflurane

In a multicenter trial, the determinants of halothane and isoflurane consumption were investigated in 212 female and 83 male patients scheduled for elective surgery (25). In a stepwise linear regression analysis, the halothane and isoflurane total consumption rates, but not the total consumptions, were influenced by gender, being higher in females than in males. As the results were not consistent among the variables studied, there is no evidence that the gender difference found is clinically significant.

In another study, the end-tidal concentrations on awakening from anesthesia with isoflurane were investigated in 18 patients scheduled for elective surgery (26). The concentrations did not correlate significantly with gender.

Sevoflurane

The effect of sevoflurane on the ventilatory response to isocapnic hypoxia was studied in 18 young healthy volunteers. A subanesthetic sevoflurane level (0.25% end-tidal concentration) reduced the hypoxic ventilatory response significantly, but there were no gender differences (27). In another study, the end-tidal concentrations on awakening from anesthesia with sevoflurane were investigated in 11 females and 10 males scheduled for elective surgery (26). The concentrations did not correlate significantly with gender.

Desflurane

In 20 young healthy volunteers, the average partial pressure of desflurane required to prevent movement in response to noxious electrical stimulation was investigated (28). Females required a 20% higher desflurane concentration than males (5.5 and 4.6 volume percent, respectively) to prevent movement at baseline conditions. However, as the gender difference disappeared during transcutaneous electric stimulation of an auricular acupuncture point, the consistency of the finding seems to be low.

In conclusion, although some of the studies are small and may thus be underpowered, no clinically relevant gender differences have been revealed for inhalational anesthetics. Thus, no specific recommendations can be given, and the need for more properly designed studies is obvious.

Intravenous anesthetics

Studies comparing gender effects were identified for midazolam, thiopental and propofol. For other

Intravenous anesthetics such as ketamine and etomidate, no information could be obtained.

Midazolam

There are conflicting results regarding the influence of gender on the pharmacokinetics of midazolam, which is metabolized predominantly by CYPs 3A4 and 3A5. One of the first evaluations studied intravenous and oral administration in 10 young and 10 elderly healthy volunteers of both genders in a randomized crossover design (28). The study focused on age more than on gender, and the number of subjects included was small. Except for a higher volume of distribution in females (difference not quantified), significant gender differences in disposition were not observed. In another study, the pharmacokinetics of midazolam and its active metabolite α-hydroxymidazolam after intramuscular administration were compared in groups of 16 young and 16 elderly volunteers of both genders in an open parallel design (30). Overall, this study confirmed the observations in the above study. In addition, elderly females had a 30% higher clearance than elderly males. The age and gender effects of a single dose of intramuscular midazolam given for premedication were also investigated in a double-blind parallel group study including 600 patients, divided into groups of 20 with respect to gender, age (three groups) and dose (five groups) (31). No differences related to gender were found. In young volunteers, others have also shown no significant gender-related differences in systemic midazolam clearance (7, 32, 33). In contrast, in a small cohort of subjects, midazolam clearance was found to be 50% greater in females compared with males (34). More recently, the relative contributions of intestinal and hepatic metabolism to midazolam clearance were studied (35). There was no effect of gender on systemic midazolam clearance, however, midazolam oral clearance was 90% higher in females (1.9 ± 1.0 vs. $1.0 \pm 0.31\,h^{-1}kg^{-1}$). In addition, in females not taking oral contraceptives, both systemic and oral clearances were higher than in males.

Gender-based differences in human liver CYP3A4 content have not been observed *in vitro* (36–38). In humans, gender differences in clearance have been revealed for some CYP3A4 substrates (39), but not for all (40). Although midazolam is known to be metabolized by CYP3A4, significant differences in its pharmacokinetics in relation to gender have not been consistently demonstrated. Thus, no specific recommendations regarding gender-specific dosage can be given.

Thiopental

Avram and coworkers (17) compared thiopental pharmacokinetics and -dynamics in 60 patients aged 18–83 years. Thiopental was infused at a rate of $150\,mg\,min^{-1}$, and time to loss of a water-filled syringe and burst-suppression was measured. Females reached the end-points at approximately 20% lower doses than did males, but when body weight and particularly lean body mass was taken into consideration, this gender effect was minimized or eliminated. Thus, this study verifies that irrespective of gender, thiopental should be dosed according to body weight with lean body mass considerations in mind.

Propofol

In a phase IV multicenter study of 2981 patients, females recovered more quickly than males from propofol (41). This was also confirmed in a recent prospective cohort study (42). Moreover, among 274 adult patients given propofol/alfentanil/nitrous oxide anesthesia, females had consistently approximately 40% shorter recovery times than males (43). The authors discussed the possibility that this observation was partly the result of the lower sensitivity to propofol in females compared with males. They provided support for this hypothesis in a small ($n = 10$) volunteer study showing that males became more deeply sedated (measured by auditory evoked potentials) than females with the same dose of propofol (44). The authors then re-examined possible gender aspects in a previous volunteer study ($n = 72$) using the bispectral index to determine the sedation level. Again, evidence of a lower sensitivity for propofol was found in females (45). In a study in 32 elderly patients, blood propofol concentrations were approximately 10% lower in females than in males (46). The pharmacokinetic analysis revealed a larger volume of distribution and a higher metabolic clearance in females. Finally, in a recent study of 20 patients undergoing laparoscopic cholecystectomy, the time from termination of propofol infusion to response to verbal stimuli was significantly shorter in females than in males, 13 vs. 19 min (47). In this study, no gender differences in propofol plasma concentrations were observed, neither at the end of surgery nor at the time of emergence.

These studies consistently show that females are less sensitive than males to the anesthetic effects of propofol resulting in 40% faster recovery in females at the same propofol dose. One of the studies (47) provides evidence that the gender difference is caused by pharmacodynamic factors, whereas another study (46) in the elderly showed that a pharmacokinetic

difference also may exist, at least in this population. Thus, the precise mechanism for the observed gender difference is not established, and further research is required to clarify this issue. Also, clinical studies designed to demonstrate whether a dose-reduction of propofol in males is safe should be encouraged.

Opioid analgesics

Studies comparing gender effects were identified for the μ (OP_3) receptor agonists morphine, ketobemidone, fentanyl, alfentanil and remifentanil, and the κ (OP_2) receptor agonists pentazocin, nalbuphine and butorphanol. For other opioid analgesics, no information could be obtained.

Morphine

The influence of anesthesia and surgery on the pharmacokinetics of morphine has been studied in six females and four males scheduled for major abdominal surgery (48). In this small study, no significant gender differences in the morphine requirements or in mean morphine plasma concentrations were revealed. Also the results from another study (49) indicate the absence of a gender influence on morphine pharmacokinetics. In this study, seven females and 14 males undergoing elective abdominal aortic reconstruction were given morphine 0.05 mg kg^{-1} intradurally. The pharmacokinetic parameters measured showed great variations between patients, but the variability could not be attributed to patient age or gender. However, both these studies are most likely underpowered in order to reveal any gender differences.

In four studies on morphine requirements in a total of 915 females and 918 males following surgery, morphine was administered as patient-controlled analgesia (50–53). In these studies, males needed on average 40% more morphine than females in order to achieve similar levels of pain relief. As morphine and morphine glucuronide concentrations were not measured, the mechanism of the observed gender difference could not be determined.

In another study (54), the influence of intravenous morphine on the hypercapnic and hypoxic ventilatory response was tested in 26 young healthy volunteers in a placebo-controlled double-blind study. After morphine administration, the females showed a 30% decrease in the ventilatory response to carbon dioxide, a 50% decrease in hypoxic sensitivity, and no change in the apneic threshold. In contrast, in the males, morphine had no significant effect on the ventilatory response to carbon dioxide or hypoxic sensitivity, and caused a small increase in the apneic threshold. Although the authors suggested that the observed differences were caused by gender differences in the pharmaco dynamic effects of morphine, morphine concentrations were not measured, and hence, pharmacokinetic differences could not be excluded.

In a recent prospective study (57), in which 1444 females and 854 males were included, morphine was given as patient-controlled analgesia for three days after predominantly abdominal or orthopedic surgery. Gender was found to be the strongest predictor overall for postoperative morphine requirements, and males needed 24%, 38% and 30% higher morphine doses than females, for each of the three study days. The morphine concentrations were not measured.

In an experimental study (19), 20 healthy females and males were given a bolus dose of 0.1 mg kg^{-1} morphine followed by 0.03 mg kg^{-1} h^{-1} for 1 h. No differences in the serum concentrations of morphine and morphine glucuronide metabolites were observed. Using an electrocutaneous pain model, baseline pain threshold (stimulus at which subjects first felt pain) and pain tolerance (maximum tolerated pain) were equal in females and males. However, a gender difference in morphine pharmacodynamics was observed. The AC_{50} (effect-site concentration causing 50% attenuation in response) for the pain threshold was 42 and 71 nmol l^{-1} in females and males, respectively, and AC_{50} for pain tolerance was 33 and 76 nmol l^{-1}, respectively. There was also a gender difference for the effect-site concentration equilibration half-life, which is a function of the equilibration time rate constant, k_{e0} (see the section 'Drug concentration at the effect site'). This parameter was more than doubled in females compared with males (38 and 1.6 h, respectively, for the pain threshold). Thus it appeared that males would require approximately 60% more morphine than females to achieve the same pain relief.

According to the recent and well-designed experimental studies it seems clear that females are more sensitive to the effects of morphine compared with males. Although clinical studies are less clear, they indicate that males require a higher dose of morphine to achieve adequate pain relief. On average, the difference in dose requirements seems to be at least 30–40%. For females as a group one may suggest that adverse effects such as respiratory depression may occur more easily when morphine is administered in the same doses as in males.

Ketobemidone

In a study in eight females and seven males, ketobemidone was given as patient-controlled analgesia

after major intra-abdominal surgery (58). No gender differences were revealed, but on the other hand, the study was not specifically designed for this purpose, and the low number of subjects provides a low statistical power for detecting any difference.

Fentanyl

In a study of 17 females and 13 males, fentanyl was given as a continuous infusion for postoperative pain. In this study, males needed approximately 25% higher doses than females to achieve the same effect (55). This finding could be explained by pharmacokinetic differences, such as a higher clearance in males, but as no such parameters were calculated in the study, the reason could also be increased pharmacodynamic sensitivity in females.

Alfentanil

Alfentanil is a substrate for hepatic CYP3A4 (56, 59) and alfentanil systemic clearance is almost entirely dependent on hepatic CYP3A4 activity (60). The volume of distribution in females is found to be 15% higher than in males (61), although the clinical significance of this small difference is probably limited (61). Large population studies and smaller investigations in volunteers showed no gender difference in alfentanil clearance in young subjects (4, 33, 61), although one study reported that clearance in young females was approximately 45% higher than in young males (12). Several investigations in both surgical patients and volunteers showed an age-dependent decrease in alfe- ntanil clearance (11, 61). Later, it was observed that the age effect might be gender related, as alfentanil clearance significantly decreased with increasing age in females, but not in males (12). In that study, 21 females and 15 males undergoing elective abdominal surgery were included. Clearance was approximately 70% higher in females aged younger than 50 years than in those aged older than 50 years, and was also 25–50% higher than in males. A subsequent analysis suggested that the decline in clearance with increasing age could be interpreted as a difference between premenopausal and postmenopausal females (62), and possibly caused by hormonal effects. However, there is no consistent evidence for a postmenopausal hormonal effect on CYP3A4 activity (see the section 'Drug elimination'), and concomitant drug administration in the older females and age-related CYP3A4 drug interactions could, at least in theory, account for the observed effects. Thus, with the present knowledge, no gender- or age-specific dose recommendations can be given, and further investigations are needed to clarify the possible gender effects on alfentanil disposition. Studies on gender differences on pharmacodynamics are lacking.

Remifentanil

The influence of gender on the pharmacokinetics and pharmacodynamics of remifentanil has been studied in 27 female and 38 male healthy volunteers (63). No differences regarding the pharmacokinetic variables or EEG variables were observed. In another study (64), 40 ASA class I–III patients undergoing elective intra-abdominal surgery were included. Remifentanil was given by continuous infusion with nitrous oxide for maintenance of anesthesia. The median remifentanil blood concentration required to achieve adequate anesthesia was 83% higher in females than in males. However, the type of surgery was different between genders. Most males underwent prostatectomy whereas the females went through various procedures. It therefore remains unclear whether gender or type of surgery was the cause of this difference. Thus, as there is no conclusive information indicating that a true gender difference exists in the pharmacokinetics or pharmacodynamics of remifentanil, no gender-specific dose recommendations can currently be given.

κ (OP_2) receptor agonists

Pentazocin has been investigated in patients with postoperative dental pain. Ten females and eight males were given pentazocin after the removal of impacted third molars. Pentazocin produced significantly greater analgesia in females than in males (23). In another study, the same group investigated the analgesic effects of nalbuphine and butorphanol (24). Twenty females and 28 males undergoing removal of third molars were studied. Also these drugs produced significantly greater analgesia in females than in males. In a third study by the same group (65) nalbuphine 5, 10 or 20 mg, or placebo, was given to 69 females and 62 males. The response to placebo was similar in females and males, but for all doses of nalbuphine, females exhibited significantly greater analgesia than males, corresponding to approximately 2 cm on a 10-cm visual analog scale. Interestingly, males reported significantly greater pain on the lowest nalbuphine dose (5 mg) than on placebo.

In conclusion, it appears that all κ receptor agonists may be less effective in males, while producing satisfactory analgesia in females. The reason for this difference remains unknown.

Benzodiazepines

Midazolam is discussed in the section intravenous anesthetics. Of other benzodiazepines of interest in

anesthesiology, studies on gender effects were identified for diazepam, oxazepam and lorazepam.

Diazepam

Single-dose pharmacokinetics of diazepam has been studied in four groups of healthy young and elderly females and males with 11 subjects in each group (66). Five to 10 mg of diazepam was injected intravenously, approximately adjusted for body weight. The volume of distribution was approximately 50% higher and the plasma clearance was 30% higher in young females than in young males. No gender differences were found in elderly subjects. In a study in nine young and 10 elderly subjects, diazepam 0.125 mg kg^{-1} was given intravenously over 10 min (67). Plasma clearance was 45% lower in females than in males, and the elimination half-life was 44% longer. No difference was found in the volume of distribution, although in the young subjects, the volume of distribution was 28% higher in females than in males.

In another study, 13 young female volunteers and 27 young and elderly male volunteers received diazepam 5–10 mg intravenously, adjusted for body weight (68). The volume of distribution was 40% higher in females than in males. The elimination half-life was nearly identical, and the plasma clearance was 30% higher in females than in males.

In a study focusing on pharmacodynamic effects of diazepam, various psychomotor tests were performed in 20 females and 20 males after intake of 10 mg diazepam or placebo orally (69). This study showed that the diazepam-induced impairment of psychomotor performance 30 and 90 min after drug intake was greater in females than in males. Whether pharmacokinetic or pharmacodynamic differences account for these results is unclear.

In conclusion, it seems that the pharmacokinetics of diazepam differs between the genders, females having a larger volume of distribution. For other pharmacokinetic parameters, the results are inconsistent. The higher volume of distribution in females is as expected for a lipid soluble drug. Accordingly, in order to achieve the same concentration after single-dose administration, the dose per kg body weight should possibly be somewhat higher in females than in males. On the other hand, females may be more sensitive to the drug effects than males (69), at least with regard to psychomotor effects. Whether these differences are of relevance for the effects in anesthesia is not known. Therefore, it is not possible on the basis of current knowledge to give any gender-specific dose recommendations.

Oxazepam

Twenty female and 18 male healthy volunteers participated in a study on oxazepam pharmacokinetics after ingestion of a single dose of 30 mg of oxazepam (70). The elimination half-life of oxazepam was 24% longer in females than in males, and the oral clearance was 29% lower. These results indicate that females need somewhat lower doses than males in order to achieve the same plasma concentration at steady state. However, the consequences of the observed pharmacokinetic observations are unclear, as no outcome variables were measured. Therefore, no specific dose recommendations can be given.

Lorazepam

The pharmacokinetics of lorazepam was studied in a group of 30 young and elderly healthy volunteers (71). Lorazepam was given intravenously at doses of 1.5–3.0 mg, adjusted for body weight. No gender differences were revealed for any of the pharmacokinetic parameters studied. Also the effect of gender on the protein binding of lorazepam was studied in the same population (72), and no gender effects were revealed.

Possible gender differences in clinical responses to lorazepam have been examined after administration of lorazepam 30 mg kg^{-1} or placebo intravenously (73). Twelve female and 16 male healthy volunteers participated in the study, in which motor coordination and the subjects' perception of sleepiness, dizziness and anxiety were evaluated. Plasma concentrations of lorazepam were similar in females and males, and no pharmacodynamic differences were observed. Thus, no clinically important differences in lorazepam pharmacokinetics or pharmacodynamics between females and males were found.

Regarding benzodiazepines as a group, gender-related differences seem small from an anesthetic point of view. Thus, gender considerations should be expected to have little impact on the dosing of these drugs.

Muscle relaxants

Studies comparing gender effects were identified for most currently approved muscle relaxants with the exception of suxamethon (succinylcholine) and mivacurium.

Vecuronium

An early and small study in 10 patients (74) showed no gender differences in sensitivity to vecuronium,

measured as per cent twitch depression after injection of vecuronium 56 μg kg^{-1} body weight. However, subsequent and larger studies have come to opposing conclusions. In a study of 40 patients undergoing routine surgery, females required 22% less vecuronium to achieve the same neuromuscular blockade as males (75). Similarly, in another study in 60 patients undergoing elective plastic surgery, the mean percentage depression of T1 (using train-of-four monitoring) was 43% greater for females at each dose of vecuronium. The dose–response curve for females was shifted to the left with ED_{50} and ED_{90} of 18 and 34 μg kg^{-1}, respectively, in females, and 24 and 45 μg kg^{-1}, respectively, in males (76). Moreover, the clinical duration was significantly longer in females than in males (37 and 27 min, respectively) after a dose of 0.08 mg kg^{-1}. A further study (77) including 80 patients undergoing elective surgery found that the intubating conditions after 60 s were better for females than for males when given the same dose of vecuronium. No differences in the time to full relaxation or in the duration of relaxation were found in this study.

Most studies indicate that the required dose of vecuronium is on average 20–30% lower in females than in males. The explanation for the gender difference in sensitivity to vecuronium appears to be pharmacokinetic (78). At equal doses, vecuronium plasma concentrations were significantly lower in males, as a result of a larger central volume of distribution (54 vs. 40 ml kg^{-1}) as well as a larger steady-state volume of distribution (201 vs. 165 ml kg^{-1}). No gender differences in clearance were observed.

Pancuronium

The onset time of neuromuscular blockade after the administration of pancuronium 0.06 mg kg^{-1} in 114 patients has been found to be statistically significant shorter in females than in males (79). The time to 90% blockade was 154 s in females and 203 s in males; a difference that most likely is also of clinical significance. The difference has, as for vecuronium, been attributed to a greater percentage of adipose tissue and thus a lower volume of distribution of these water-soluble drugs in females. In contrast, in a much smaller study (10 patients), no gender differences were seen in per cent twitch depression after injection of pancuronium 64 μg kg^{-1} body weight (74), but it can be questioned whether this study was sufficiently powered. One may thus conclude that although the tendency for pancuronium is the same as for vecuronium, less clear data are available and the possible gender difference is not adequately quantified.

Rapacuronium

In a study on rapacuronium pharmacokinetics, 28 females and 15 males ASA class I–III were investigated (80). There were no differences in clearance between females and males. Thus, although the data are very sparse and there is a risk of type II errors in the only published study, current data do not suggest any gender-specific dose recommendations.

Atracurium

In a study in 41 otherwise healthy patients undergoing minor surgery, atracurium clearance was lower and elimination half-life was longer in females than in males (81). Although statistically significant, an absolute difference of 1.9 min is expected to be clinically insignificant compared with the mean elimination half-life of 20 min.

In another study, the same authors examined the effect of gender on the pharmacodynamics of atracurium in 21 female and 17 male patients undergoing minor surgery (82). The concentrations that produced 50% neuromuscular blockade and the highest concentrations that failed to provoke any effect did not differ between females and males. This is consistent with the results in another study on 10 patients, in which no gender difference in sensitivity to atracurium was found, measured as per cent twitch depression after injection of atracurium 276 μg kg^{-1} body weight (74). As the number of subjects in this study, however, was very low, there is a high risk for a false negative result.

Cisatracurium

Possible gender effects on the disposition of cisatracurium have been studied by a population pharmacokinetic/pharmacodynamic approach where data from 241 patients in eight prospectively designed phase I–III trials were pooled and analyzed (83). The results showed that gender as a variable produced small, but statistically significant changes in some of the pharmacokinetic parameters. These changes were not associated with any clinically significant alterations in the predicted onset or recovery profile for cisatracurium, and they therefore do not warrant any gender-specific dose recommendations.

Rocuronium

Gender differences in the dose–response relationship and in the time course of the effect of rocuronium have been studied in 60 adult patients scheduled for elective plastic surgery (84). The dose–response curve for females was shifted to the left with ED_{50}, ED_{90} and

ED_{95} values of 128, 252 and 274 μg kg^{-1}, respectively, in females, and 178, 358 and 386 μg kg^{-1}, respectively, in males. The neuromuscular block was significantly prolonged in females, with the duration of peak effect, clinical duration and total duration being 11.8, 18.5 and 46.8 min, respectively, in females, and 6.5, 12.5 and 35.6 min, respectively, in males. The results from this study thus clearly suggest that females are more sensitive than males, requiring approximately 30% less rocuronium to achieve the same degree of neuromuscular block, and imply that the rocuronium dose should be reduced in females compared with males.

In conclusion, it is reasonably well documented that females require less vecuronium and rocuronium than males. This may also well be true for pancuronium, but is not as clearly demonstrated as for vecuronium and rocuronium. The mechanism is most likely pharmacokinetic and explained by gender differences in the volume of distribution. One may speculate that as the properties related to distribution in the body are quite similar for all muscle relaxants, it might well be the case that significant gender differences will be found also for the other drugs when adequately designed and sufficiently powered studies are carried out.

Local anesthetics

Studies comparing gender effects were identified for lidocaine. For other local anesthetics, no studies on possible gender differences were found.

Lidocaine (lignocaine)

In a study on lidocaine pharmacokinetics in young and elderly healthy volunteers, nine young and seven elderly females and 15 young and six elderly males received a single dose of lidocaine 25 mg intravenously (85). The volume of distribution was 33% higher in young females than in young males and 19% higher in elderly females than in elderly males, and was not influenced by age. In contrast, the elimination half-life was prolonged and the clearance was reduced in elderly males as compared to young males and females. In another study on the pharmacokinetics of lidocaine after intravenous injection, 18 healthy volunteers aged 18–33 years received a single bolus dose of 75 mg or 100 mg according to body weight (86). Females had a 62% larger volume of distribution and a 50% longer elimination half-life than males. There were no differences in clearance.

In a study in 30 female and 21 male asthmatic volunteers (87), topical upper airway anesthesia with lidocaine was given before research bronchoscopy and serum lidocaine concentrations were measured 30 min after the anesthesia and 30 min after the bronchoscopy was completed. No differences in serum lidocaine concentrations were found between genders, but on the other hand, the study was not specifically designed to reveal such differences.

Taken together, the results from these studies indicate that females have a larger volume of distribution than males. Consequently, females may require a higher intravenous bolus dose of lidocaine to achieve the same plasma concentration and possibly also the same initial therapeutic effect, but the data are too scanty to suggest any gender-specific dose recommendations. For topical and other non-intravenous use, differences in the volume of distribution would not be expected to have any significant impact on the therapeutic effect.

Adrenergic agonists and antagonists

Studies comparing gender effects for adrenergic antagonists and agonists of relevance in anesthesia were identified for the beta-receptor antagonists propranolol and metoprolol and for some alpha-adrenergic and beta-adrenergic agonists.

Propranolol

In a study of biological determinants of the disposition of propranolol in more than 1300 patients, gender was shown to be the most important predictor of the serum propranolol concentration, which on average was found to be 79% higher in females than in males (88). In a subsequent study, oral clearance of propranolol was found to be 80% higher in males than in females (89). It should, however, be noted that in these studies propranolol was given as a racemate and the total concentration was measured even though only the S-enantiomer is biologically active. Moreover, the findings were not correlated to a relevant outcome. In a later study of 24 healthy volunteers, the stereoselective pharmacokinetics of propranolol was investigated (90). In this study, males had 45% higher clearance of the inactive R-enantiomer than females, whereas the difference in clearance of the active S-enantiomer was not statistically significant. Thus, one may speculate that the increase in the total clearance seen in males in the two previous studies (88, 89) was caused by an increase in the biotransformation of

the inactive enantiomer, indicating that the observed differences in total clearance and total serum concentration may not have any clinical significance.

Metoprolol

The pharmacokinetics and pharmacodynamics of metoprolol have been studied in 20 healthy volunteers given a total of nine oral doses of metoprolol 100 mg (91). The results showed that females had an oral clearance that was approximately 50% of that in males both for the active S-enantiomer and the inactive R-enantiomer. The concentration-effect curves for males and females were identical, and consequently, females experienced a significantly greater reduction in exercise heart rate than did males. Thus, gender differences seem to exist in the pharmacokinetics of metoprolol causing variations in the serum concentrations that may result in an increased effect in females.

Adrenergic agonists

Gender-related differences in pharmacokinetics and effects of the adrenergic agonists isoprenaline (isoproterenol), phenylephrine and clonidine have been elucidated in several studies in healthy volunteers (92–95). For other adrenergic agonists, no studies were identified. The results are in many aspects inconsistent. Regarding the beta-adrenergic agonist isoprenaline, females were less sensitive in two studies (92, 95) whereas males were less sensitive in the third study (94). In a fourth study, the age-related decline in sensitivity to isoprenaline was more pronounced in males than in females (96). For the alpha-adrenergic agonists phenylephrine (an α_1 receptor agonist) and clonidine (an α_2 receptor agonist), there are also some discrepancies between studies (92, 93, 97), but most evidence suggest a decreased receptor sensitivity in females. Some of the discrepancies could be explained by differences in methodology, including the doses given and the types of end-points. In the study in which no differences were observed (93), the number of subjects included was very low, with a correspondingly high risk of type II errors.

Taken together, available data may suggest that alpha- as well as beta-adrenergic agonist responsiveness could be lower in females than in males, although there are considerable inconsistencies between studies. It is, however, interesting that in one of the studies (92), no responses at all were seen in females after infusion of isoprenaline, phenylephrine and clonidine. Further studies, particularly on more frequently used drugs such as ephedrine, dopamine, dobutamine, adrenaline (epinephrine) and noradrenaline (norepinephrine) are clearly needed before any firm conclusions can be drawn.

Non-opioid analgesics

Studies comparing gender effects were identified for paracetamol, acetylsalicylic acid and ibuprofen. For other non-opioid analgesics, such as diclofenac, ketorolac and the cyclooxygenase (COX)-2 inhibitors, no studies on possible gender differences were identified.

Paracetamol (acetaminophen)

The effects of gender and obesity on paracetamol pharmacokinetics were examined in 21 obese and 21 normal-weight subjects of both genders after intake of a single dose of 650 mg (98). Females displayed almost 30% lower clearance and volume of distribution compared with males. In another study (99), a single dose of paracetamol 1 g was given to young healthy females and males as well as young females using oral contraceptives ($n = 8$ in each group). The findings in the two control groups confirmed the above observations, although the results were less pronounced in this sample. Users of oral contraceptives had a 50% higher clearance both for the conjugation and the oxidation pathways compared with control females.

The primary route of elimination for paracetamol is glucuronide and sulfate conjugation. However, also oxidation by CYP enzymes to the hepatotoxic metabolite takes place and is increased in females on oral contraceptives. Again, oral contraceptives seem to offset a gender difference in the disposition of drugs metabolized by conjugation. Whether the observed differences affect efficacy and safety remains unsettled.

Acetylsalicylic acid (aspirin)

Gender differences in the pharmacokinetics of salicylate have been addressed in several studies. In a study in 50 volunteers, no other differences than a longer time to maximum serum concentrations in females than in males were found (54 vs. 32 min) (100). In another study, 16 volunteers were given a single oral dose of acetylsalicylic acid 14.3 mg kg^{-1} body weight and eight volunteers were given 14.3 mg kg^{-1} body weight every eighth hour for 7 days (101). Peak plasma concentrations of salicylate in females were almost 50% higher than in males. Moreover, oral clearance was 40–60% lower in females than in males. In another study, it was confirmed that females had higher peak plasma concentrations than males

after single dosing of 650 mg acetylsalicylic acid (102). However, in yet another single-dose study including 44 healthy subjects, no clinically significant pharmacokinetic differences were observed between the genders (103).

The above-cited pharmacokinetic data from healthy subjects are conflicting, although clearance may be somewhat lower in females. However, further studies are clearly needed before any firm conclusions can be drawn.

Ibuprofen

The active enantiomer S-ibuprofen is metabolized by CYP2C9 and undergoes in addition glucuronidation. Most of the inactive R-enantiomer in the racemic drug formulation is metabolized to the active S-enantiomer. In 16 young healthy volunteers, no pharmacokinetic differences were revealed between females and males, including females on oral contraceptives (104). In a placebo-controlled, double-blind cross-over study of experimental pain (105), the effect of ibuprofen 800 mg was investigated in 20 subjects. Serum concentrations of ibuprofen were also determined. Females had a two-fold greater volume of distribution when body weight was taken into consideration. Females also felt pain more easily than males when given placebo and did not respond to ibuprofen. In contrast, males experienced even higher pain thresholds when given ibuprofen.

In conclusion, no clinical significant gender difference in the pharmacokinetics of ibuprofen has been found. When it comes to pharmacodynamics, although experimental, a significant gender difference has been observed in one study. This observation should generate further studies in patients to clarify whether such a gender difference may have clinical implications.

Glucocorticoids

Prednisolone

In a study of eight healthy volunteers given a single intravenous dose of prednisolone 0.075 mg kg^{-1} body weight, clearance in females was approximately 30% higher than in males (106). This tendency could be explained by the fact that most steroid molecules seem to be metabolized by CYP3A4, which might have a higher activity in females. Although the study is very small, the gender difference found could indicate that females may need higher doses than males in order to achieve the same clinical response. However, as shown for methylprednisolone (107), females may be more sensitive for the effects of glucocorticoids than are males, thus indicating a possibly similar or close to similar clinical response when given the same dose.

Methylprednisolone

The pharmacokinetics and pharmacodynamics of methylprednisolone have been studied in six menopausal females and six males (107). The total clearance of methylprednisolone was 55% higher in females than in males, and the terminal elimination half-life was 1.7 h in females and 2.6 h in males. Evidence was also found indicating that females were more sensitive than males, as the mean inhibitory concentration for 50% suppression of cortisol secretion was considerably lower in females (0.1 vs. 1.7 ng ml^{-1}). This study demonstrates gender differences both in the pharmacokinetics and the pharmacodynamics of methylprednisolone. Although females had lower plasma concentrations than males, they were more sensitive to the drug, thus indicating the possibility of an increased, decreased or similar net response.

In conclusion, although some gender differences may exist, no recommendations regarding gender-specific dosing of glucocorticoids can be given from this small base of knowledge.

Other drugs

Tirilazad

Clinical trials of the non-glucocorticoid steroid tirilazad in subarachnoid hemorrhage have demonstrated clear differences in outcome between females and males (108, 109). In both these studies, no beneficial outcome was shown in females in contrast to that in males. The reason for this observation seems to be pharmacokinetic differences between genders. CYP3A4 has an important role in the elimination of tirilazad and its active metabolite (9, 110). In the latter study, premenopausal females cleared tirilazad 50% faster than postmenopausal females. The difference was not reversed by postmenopausal hormone replacement. Moreover, after intake of single doses, female volunteers seem to clear tirilazad more rapidly than male volunteers, particularly among the younger subjects where females had 40% higher clearance than males (111). However, this gender difference has been less impressive in multiple-dosing studies and in population kinetic analysis (112–114), indicating that pharmacodynamic differences also may contribute (115). Clinical trials in females with doses two to three times higher than in males have shown pos-

itive effects on outcome (vasospasm or mortality) similar to those observed in males, at least in some subgroups of females (116, 117). Thus, with respect to medication with tirilazad gender must clearly be taken into consideration.

Conclusions and future aspects

In general, the base of knowledge on gender differences of anesthetic drugs is small. One explanation is probably that clinical investigators historically have been more or less reluctant to include females in clinical trials because of concerns with potential birth defects, not least caused by discriminating guidelines and regulations from bodies responsible for drug approval procedures.

The present documentation shows that gender differences in the pharmacokinetics and pharmacodynamics for some drugs used in the practice of anesthesia do exist. Isolated pharmacokinetic observations should not lead to altered clinical practice, as a pharmacokinetic gender difference might be counterbalanced by a pharmacodynamic difference in the opposite direction. If pharmacokinetic differences of relevance for the outcome are demonstrated, anesthesiologists should be aware that in general, differences in the volume of distribution call for a change in the practice of the initial loading of the drug, while differences in clearance require adjustments in the maintenance infusion rate. However, group differences of less than 20–30% are most often not relevant in clinical practice.

Pharmacokinetic gender differences are seen for some drugs undergoing glucuronidation, such as paracetamol and oxazepam. Furthermore, females have approximately 20–30% greater sensitivity for the muscle relaxing effects of vecuronium, pancuronium and rocuronium, most likely because of a smaller volume of distribution. When a rapid onset of action is required, one should consider increasing the dose in males compared with females. Conversely, a reduction in the dose for females should be the consequence if short duration is the primary goal of a single dose of vecuronium, pancuronium and rocuronium administration.

The extensive scientific efforts by means of adequately conducted studies experimentally and clinically seem to confirm some gender differences for drugs metabolized by CYP3A4, although *in vitro* studies have not revealed a higher CYP3A4 activity in females. In clinical studies, many drugs metabolized by CYP3A4, such as alfentanil and tirilazad, have demonstrated a 50–70% higher clearance in young females compared with young males, although the gender differences may be lower in the elderly. However, only for tirilazad it is conclusively demonstrated that the gender difference in clearance has consequences for outcome.

When gender differences in pharmacodynamics are observed, these should also be interpreted with caution. It should first be considered whether the study has chosen a relevant endpoint, and second whether the investigated sample is representative for the clinical population. For example, a lower clearance of the active form of metoprolol resulted in a lower heart rate in healthy female volunteers, but this has not been shown in patients. Another example is experimental pain. Are differential effects in young healthy volunteers a sufficient base to suggest that clinical practice should be changed? In our opinion, practice should not be changed unless evidence is established in studies with patients in the operating theater or at other venues relevant for anesthesia. One such example is propofol, for which females are less sensitive than males. It may be prudent to reduce the dose in males by 30–40% of the female dose to achieve similar recovery times.

A gender difference in sensitivity opposite that of propofol is found for some opioids. Females are significantly more sensitive to the κ (OP_2) receptor agonists pentazocine, nalbuphine and butorphanol. Similar observations have also been seen for morphine. Female volunteers display a greater sensitivity to morphine than males, and it is calculated that males need morphine doses 60% higher than females to achieve equivalent pain relief. Clinical data are less clear, but a majority of studies on patient-controlled analgesia has shown that males require more morphine than females. On this basis, males should be expected to require more morphine than females to achieve adequate pain relief. On the other hand, females may experience respiratory depression more easily than males.

By and large, significant gender differences are recognized for the major groups of anesthetic drugs such as propofol, opioids and muscle relaxants. Many of these have narrow therapeutic indices and are given as infusions, which should be accurately monitored in order to achieve and maintain the desired effects. The most advanced infusions are the target-controlled infusions (TCI). Apparently there is a need for research to solve whether gender differences should be incorporated in the software of these devices.

The emerging knowledge on gender differences relevant for pharmacotherapeutics has changed the attitudes of drug-regulating authorities, which have now issued guidelines and regulations ensuring that

females are included appropriately in clinical trials. For example, the Food and Drug Administration (FDA) in the USA issued a guideline on this issue already in 1993. The final rule, proposed in 1998 and effective from July 2000, permits the FDA to delay a proposed clinical investigation or to suspend an ongoing trial if females or males are excluded from participation solely because of a potential risk of reproductive or developmental toxicology from the drug (128). Hopefully, such guidelines and regulations will increase the awareness of the importance of performing clinical studies with both genders adequately represented and of designing specific studies with the primary aim of revealing possible gender differences. In the future, such studies should preferably be carried out before new drugs are launched.

The effects documented in the present review clearly indicate that gender should be taken into account as a predictive factor for the dosage of several drugs used in the practice of anesthesia. There is an obvious need of more research in this field in order to further optimize drug treatment towards a more individualized dosage in anesthesia.

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