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Why do women wake up faster than men from propofol anaesthesia?

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Background. It has repeatedly been shown that female patients wake up faster from propofol anaesthesia than male patients. The reason for this is not clear. It is possible that female patients have a more rapid decline in plasma propofol concentration after termination of an infusion, or there could be gender differences in the sensitivity to propofol, making women wake up at higher concentrations. We tested the hypothesis that women wake up faster because of a more rapid decline in plasma propofol.

Methods. Sixty adult patients (30 female and 30 male; ASA I or II) undergoing lower limb surgery under regional anaesthesia, were enrolled in an open study. Propofol was given as the only hypnotic drug, administered by the plasma target control system (TCI) Diprifusor®, titrated to bispectral index (BIS) values of 40–60. Blood samples for propofol measurements were taken just before the propofol infusion was stopped and when the patients woke up.

Results. The female patients woke up faster than the male patients (5.6 *vs* 8.2 min, P=0.003). The plasma propofol concentration declined more rapidly in the women (P=0.02). An additional significant finding was that the TCI algorithm had a better fit for the women than for the men, with a median prediction error (MDPE) of 2% in the female patients compared with 40% in the male patients (P<0.001). At emergence the men had a significantly higher measured propofol concentration than the women (P=0.05).

Conclusion. The female patients had a more rapid decline in plasma propofol at the end of infusion. Gender differences in pharmacokinetics could explain the faster emergence for female patients after propofol anaesthesia, and gender differences in propofol sensitivity may also be present.

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Individual variation in the pharmacokinetics and dynamics of intravenous anaesthetics is considerable. A given dose of an anaesthetic, even if adjusted to weight, results in a huge variation in plasma concentration in the individual patient (i.e. pharmacokinetic variability). Further, at a given serum concentration there is wide fluctuation in the effect achieved in different patients (i.e. pharmacodynamic variability).

Several studies have shown that female patients wake up faster from propofol anaesthesia.[1–4] Although propofol has been used as the major hypnotic drug, additional drugs with known sedative effects, such as opioids and nitrous oxide, have been present in all these studies.

Results from a previous study using propofol and remifentanil suggested that female patients might have a more rapid decline in plasma propofol during emergence. Therefore different propofol kinetics, at least as in part, might be the explanation for the faster emergence in women.[3] The other possible explanation for a faster emergence could be a lower sensitivity to propofol in women (pharmacodynamic difference).

In order to ascertain whether gender differences in pharmacokinetics or pharmacodynamics are relevant during propofol emergence, we tested the hypothesis that female patients wake up faster than male patients because of a more rapid decline in plasma propofol concentration during emergence. In order to avoid confounding influence from other centrally acting sedatives, we tested a setting with propofol as the only hypnotic drug administered to patients with adequate spinal anaesthesia during surgery. Further, we aimed at keeping the hypnotic effect of propofol constant and similar in all patients by adjusting the propofol

infusion according to a fixed effect endpoint, which was a predefined target value of the bispectral index (BIS) in all patients.

Materials and methods

After approval from the regional committee for medical research and written informed consent, 30 female and 30 male patients were enrolled in an open study. The patients (aged 18–60 yr, ASA I or II) were admitted for surgery in the lower limbs distal of the hip which was expected to last for 1–2 h. The patients were excluded if they had any psychiatric, neurological or liver disease, if they used any regular medication with a sedative effect or any medication that is known to interact with propofol metabolism. Excessive alcohol drinkers, drug abusers and very thin or obese patients (BMI values <18 or >33) were also excluded. Women were excluded if they had passed the menopause. Zopiclone up to 7.5 mg orally the night before was accepted; otherwise intake of any sedatives for the last 24 h led to exclusion.

The patients received no premedication except oral acetaminophen 1.5–2.0 g according to body weight. In the operating room the patients had standard monitoring (ECG, non-invasive blood pressure and pulse oximetry). A venous cannula was placed in one forearm, and 500 ml Ringer's acetate was given before the spinal block was established. The crystalloid infusion was continued throughout surgery.

Spinal anaesthesia was placed in the L2–L3, L3–L4 or L4–L5 interspace with the patient in the sitting or side position. Isobaric or hyperbaric bupivacaine 5 mg ml^{-1} was chosen on the basis of expected duration of surgery and whether or not a residual analgesic effect was required postoperatively.

When the regional anaesthesia was found to be adequate, and the level for the sensory block was identified and noted, a BIS monitor (Aspect 2000, Aspect MSI, Newton, MA), software version 2.12, was connected. The impedance was checked and accepted if it was <10 kΩ. Then, hypnosis was induced by propofol, administered by the Diprifusor® serum target control (TCI) system (Alaris MSI, San Diego, CA), based on the kinetic parameters published by Marsh and colleagues.[5] The initial blood target concentration was set to 6 μg ml^{-1} and adjusted as required to send the patient to sleep, which was defined as being non-responsive to verbal commands and mild shaking (Observer's Assessment of Alertness and Sedation [OASS] score ⩽1).[6] The surgery started when the patient was asleep. The blood target concentration of propofol was adjusted throughout surgery to keep BIS between 40 and 60, and as close to a mean value of 50 as possible. The patients were manually ventilated with oxygen–air until they regained spontaneous ventilation. An airway support (e.g. a jaw support, an oropharyngeal airway or a laryngeal mask) was used if necessary. End-tidal carbon dioxide was recorded.

Prophylactic antibiotics (cephalotine 2 g i.v.) and ketorolac 30 mg i.v. for postoperative analgesia were given if required. Atropine 0.5 mg, or preferably glycopyrron 0.2 mg, was given if bradycardia, defined as persisting heart rate <40 beats min^{-1}, or excessive salivation occurred. Hypotension, defined as blood pressure <85 mm Hg, was treated with ephedrine 10 mg i.v., repeated if necessary. Bupivacaine for postoperative analgesia was administered locally by the surgeon at the end of surgery. The patient was excluded from the study if any other medication, including additional analgesics, had to be given.

Towards the end of the surgery a venous cannula for sampling blood was inserted in the elbow contralateral to the propofol infusion site. In advance, the skin had been anaesthetized topically with prilocaine–lidocaine cream (Emla®).

No adjustments were made to the target concentration of propofol during the last 15 min of surgery. The TCI infusion of propofol was abruptly terminated when the surgery was completed. At that time (T_1) the BIS level and the actual target concentration of propofol were recorded, and blood for later analysis of plasma propofol was sampled just before termination of the infusion. The patients were then awakened by being addressed by name and asked every 30 s: 'Are you awake? Can you open your eyes if you hear me?' At the time (T_2) when the patients opened their eyes on command or confirmed being awake verbally or by nodding, the same measurements (actual BIS, estimated blood propofol concentration and venous blood sample) were repeated. Emergence time was defined as the interval between T_1 and T_2. The patients were asked 4 h postoperatively if they had any memory of the operation.

Blood for propofol analysis was sampled directly into heparinized tubes and refrigerated until centrifugation which was performed within a few hours. The plasma was then transferred to storage tubes with no additional contents and frozen at −18°C. Propofol in plasma was determined in the Department of Clinical Chemistry, Ullevaal University Hospital, using a high-pressure liquid chromatography (HPLC) method with fluorescence detection.[7 8] The limit of quantification was 2 ng ml^{-1}, and the coefficient of variation (CV) was <5% over the concentration range examined.

In a previous study we found a trend towards a gender difference in plasma propofol of 0.8 μg ml^{-1} at termination of anaesthesia, but no gender difference in plasma propofol at awakening, indicating that a difference in kinetics could at least partly explain the difference in emergence time.[3] With a possibility of a two-sided outcome, a significance level (P-value) of 0.05 and a power of 0.80, we found that a minimum of 29 patients of each gender would be necessary to reveal a gender difference in the decline rate similar to or greater than that in the previous study.

Gender differences in patient characteristics, level of regional anaesthesia, emergence time, duration of the infusion, total propofol consumption, estimated and measured

propofol concentrations and BIS levels at T_1 and T_2 were all compared with independent sample *t*-tests after checking for normal distribution of the datasets. Data for these parameters are given as mean (range) or mean (SD) unless stated otherwise.

As serum propofol is expected to decline according to first-order pharmacokinetics, the average decline rate *k* for the emergence period was calculated by transforming the measured concentrations of propofol into their logarithmic values. This model represents a true simplification, as any multi-exponential influence on the slope in the immediate post-infusion phase is ignored:

$$k = \Delta(\ln[s\text{–prop } T_2] - \ln[s\text{–prop } T_1])/\text{emergence time}.$$

The gender difference in the propofol decline rate *k* was not normally distributed and therefore was analysed using the Mann–Whitney *U*-test.

To search for gender differences in the precision of the Diprifusor® we calculated the median prediction error (MDPE) and median absolute prediction error (MDAPE)[9]

$$[(C_{\text{measured}} - C_{\text{estimated}})/C_{\text{estimated}}] \times 100\%.$$

MDPE is a signed value, illustrating whether the algorithm over- or underpredicts the measured level, whereas MDAPE takes into account the absolute value of the difference and thereby represents the precision. MDPE and MDAPE are given as median (IQR), and the gender difference was analysed using the Mann–Whitney *U*-test. A *P*-value $\leqslant 0.05$ was considered significant.

Results

There was no difference between the genders with regard to age, BMI or ASA classification, but the female patients were significantly smaller (i.e. lighter and shorter) (Table 1). The mean duration of the propofol infusion was 98 (40) min, with no gender difference (Table 2). There were no significant differences between the groups in blood pressure or heart rate during the study.

The absolute difference between the asleep and awake plasma concentrations of propofol did not differ between men and women (the decline in propofol during emergence was 1.7 μg ml^{-1} in both genders), but the decline was significantly faster in the women because of the shorter emergence time (Table 3 and Fig. 1).

The mean weight-adjusted infusion rate of propofol did not differ between men and women (Table 2). Despite similar amounts of propofol infused, adjusted for the patient's weight and the duration of the infusion, men tended to have higher measured values of propofol at termination of anaesthesia (*P*=0.06) which reached significance at awakening (*P*=0.05) (Table 3 and Fig. 1).

The mean predicted and mean measured values of propofol are shown in Figure 1, which illustrates different fits to the TCI algorithm by men and women. The Diprifusor® indicated a tendency towards a lower predicted propofol level in men than in women (*P*=0.07) at termination of anaesthesia, which was opposite to the measured results. The gender difference in the predicted level of propofol at the time of awakening was significant (*P*=0.001).

The median (IQR) of the pooled MDPE for all the propofol samples with available corresponding TCI values (59 observations for each gender) was 40 (15–68)% for men and 2 (−14 to 25)% for women (*P*<0.001). MDAPE was 40 (18–68)% for men and 17 (9–32)% for women (*P*=0.001). All the corresponding data points for predicted and measured propofol concentration are shown in Figure 2. Almost all the measured propofol concentrations for the men appear to be higher than predicted, while the data points for women were distributed above and below the line of identity. This fits with the calculated MDPE for the women being close to zero.

Table 3 shows that the men and the women were anaesthetized to the same quite deep hypnotic level, based on BIS values of ∼45 in both genders at the time that the propofol infusion was terminated. The men appeared to have a higher measured propofol concentration than the women at both T_1 (termination of the infusion) and T_2 (awakening). The difference was close to significance at T_1 (*P*=0.06), and fulfilled the significance criteria on awakening (*P*=0.05), still without any gender difference in the corresponding BIS values.

Zopiclone was taken by three patients of each gender the night before inclusion. Glycopyrron 0.2 mg was given to three male and four female patients because of excessive salivation. One male patient received atropine 0.5 mg

Table 1 Patient characteristics. Data are presented as mean (range) or mean (SD) except for ASA classification. The awake BIS values were recorded after application of spinal anaesthesia

	Male (*n*=30)	Female (*n*=30)	*P*-value
Age (yr)	36.5 (22–60)	33.6 (22–47)	0.15
Weight (kg)	84 (10)	70 (9)	<0.001
Height (cm)	181 (6)	170 (4)	<0.001
BMI (kg m^{-2})	25.5 (2.7)	24.5 (3.1)	0.18
ASA I/ASA II	21/9	25/5	0.23
Awake BIS values	97 (1)	98 (1)	0.39

Table 2 Gender differences in possible confounding factors. Data are presented as mean (SD). T_1, time of termination of propofol infusion

	Male (*n*=30)	Female (*n*=30)	*P*-value
Upper level of regional block (thoracic dermatome)	8.7 (1.6)	9.4 (2.0)	0.11
End-tidal carbon dioxide at T_1 (kPa)	5.6 (0.7)	5.8 (0.8)	0.20
Duration of propofol infusion (min)	97 (43)	99 (36)	0.83
Amount of propofol infused (mg kg^{-1} min^{-1})	0.17 (0.03)	0.18 (0.04)	0.11

Table 3 Gender differences during emergence. T_1, time when the propofol infusion was stopped; T_2, time when patients woke up; k, constant describing the decline in propofol concentration between T_1 and T_2. Student's t-tests was used for all comparisons, except k, where the Mann–Whitney U-test was used. Data are presented as mean (SD) except k which is given as median (IQR)

	Male (n=30)	Female (n=30)	P-value
Awakening time (min) (T_2–T_1)	8.2 (3.7)	5.6 (2.4)	0.003
BIS at T_1	45 (10)	45 (7)	0.88
BIS at T_2	79 (5)	76 (8)	0.20
Predicted propofol concentration at T_1 (μg ml^{-1})	3.6 (0.9)	4.0 (0.9)	0.07
Predicted propofol concentration at T_2 (μg ml^{-1})	1.8 (0.5)	2.3 (0.6)	0.001
Measured propofol concentration at T_1 (μg ml^{-1})	4.8 (1.4)	4.2 (1.3)	0.06
Measured propofol concentration at T_2 (μg ml^{-1})	3.1 (1.3)	2.5 (0.8)	0.05
k	0.052 (0.032–0.102)	0.097 (0.061–0.132)	0.02

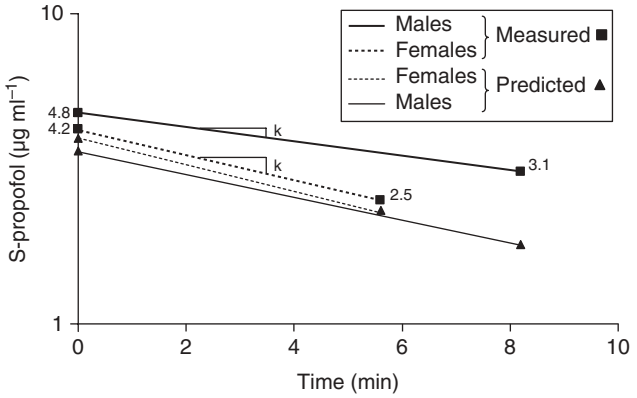

Fig 1 Decline in measured plasma concentration, and corresponding decline in the predicted plasma propofol concentration in a semilogarithmic plot. The emergence time was shorter for the women, and the decline in measured plasma propofol was more rapid. The predicted and measured lines are closer for women than for men, indicating that the TCI algorithm fits better for the women.

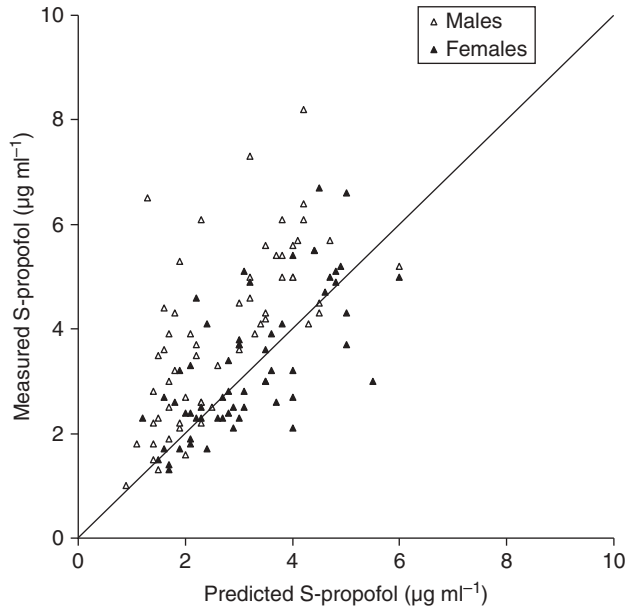

Fig 2 Predicted propofol values and the corresponding measured propofol values are shown for each gender. The line is the expected line-of-indentity between predicted and measured values.

immediately after the spinal anaesthesia because of bradycardia and near-fainting, while one woman suffered from bradycardia and hypotension after the spinal anaesthesia and was treated with glycopyrron 0.2 mg and ephedrine 20 mg.

Laryngeal masks were required for 23 of the female patients and 24 of the male patients, while one female patient and two male patients required oropharyngeal airways during surgery.

None of the patients reported any memory of the operation either spontaneously or when asked 4 h after emergence.

Discussion

The present study confirms that women wake up faster than men after propofol anaesthesia. The results strongly suggest that a gender difference in the decline of serum propofol could at least partly explain this more rapid emergence. It also appears that the Diprifusor® algorithm fits better for women than for men in the present setting. In addition, there may be a pharmacodynamic gender difference with less drug sensitivity (i.e. higher plasma concentration needed) for males at both endpoints tested (BIS=45 or the moment of awakening).

A faster emergence for women from propofol anaesthesia was shown in 1993 by Apfelbaum and colleagues[1] in a multicentre trial. A retrospective analysis of nearly 15 000 patients revealed that male gender was a strong predictor for prolonged awakening.[1] Three more recent studies have confirmed that women wake up faster than men after propofol anaesthesia.[2–4] In the first two of these studies, as well as in the study by Apfelbaum and colleagues,[1] the data were recorded without focus on a possible gender difference during the emergence phase. This is an important point, since otherwise the awakening could have been biased by the investigator's expectations. The gender difference in emergence time was highly significant in all three of these studies. The size of the difference was also considerable, with an average increase in emergence time of ∼50% in men compared with women (11 *vs* 7 min, 19 *vs* 12 min and 12 *vs* 7 min).

A faster emergence for women was also demonstrated retrospectively by Myles and colleagues[10] in a cohort

study of 463 patients anaesthetized with various combinations of drugs, including propofol, pentobarbital, sevoflurane and isoflurane. The patients were not grouped according to the different anaesthesia regimens, and so it is not clear whether the difference in emergence time also holds for volatile anaesthetics or is restricted to propofol-based anaesthesia. However, a recent study by Tercan and colleagues[11] showed that early recovery times were longer for female patients than for male patients after anaesthesia based on sevoflurane or desflurane.

The aim of the present study was to elucidate whether kinetic gender differences are present during early emergence. No previous study has focused directly on this issue in a setting with propofol as the only hypnotic agent.

Various studies addressing detailed multicompartmental propofol kinetics have not included gender influence as a part of the study hypothesis, and no definite conclusion can be drawn on gender as a relevant covariate in the post hoc analyses. An early study of 50 surgical patients by Shafer and colleagues[12] showed that female patients had higher clearances of propofol and higher distribution volumes compared with the male patients. This is in agreement with our data on males having higher measured plasma concentration than females, despite similar propofol dosing. Schnider and colleagues[13] have suggested that propofol kinetics is dependent on gender, as the clearance is indirectly affected by the relatively smaller lean body mass in women. In Schnider's model the central clearance is enlarged in women compared with men. In contrast with these results, Schuttler and Ihmsen[14] were unable to recognize gender as an independent covariate when investigating propofol kinetics in 270 individuals (150 males and 120 females). The Marsh model,[5] which is incorporated in the Diprifusor®, does not include gender as a covariate.

Vuyk and colleagues[15] studied patients aged >65 yr and concluded that gender significantly affects the pharmacokinetics of propofol in the elderly. Their results revealed a larger peripheral volume of distribution and a higher metabolic clearance, but a reduced rapid peripheral clearance, in elderly women compared with elderly men. They concluded that elderly females should be given ~10% higher infusion rates than elderly males to ensure the same blood propofol concentration. The results from our study suggest that this is also true for younger women.

There are at least three possible explanations for a faster decline in plasma propofol after an infusion of duration 1–2 h: women may metabolize propofol faster than men, women may have a faster distribution of drug from serum to tissue that is not yet saturated with propofol, or there might be a slower redistribution back to blood from saturated peripheral tissues in the immediate post-infusion phase. These issues are not clarified in the literature, and our study also leaves an open question about the explanation for the faster decline in plasma propofol.

We found that the predicted propofol values were closer to the measured values for women than the men, which is reflected in the considerably smaller MDPE for women (2% *vs* 40%). We used the Diprifusor®, which is based on the kinetics published by Marsh and colleagues.[5] This TCI system is widely used.[16] The microconstants implemented in the Diprifusor® were originally obtained from a study of only 18 patients, of whom five were females, undergoing surgery under regional anaesthesia,[17] while the value for the initial volume of distribution was obtained from a pilot study [5] and gender was not a covariate. Whether this gender discrepancy in Diprifusor® precision is similar in other patient populations or clinical settings or when opioids are used in combination with propofol remains to be studied.

It has been demonstrated that female patients require more propofol to achieve the same depth of anaesthesia, monitored by BIS or Narcotrend.[18 19] Kraus and colleagues[19] also analysed retrospectively anaesthesia records from 1000 patients in whom the infusions were adjusted without the use of a sleep monitor, and found that the women (n=383) were given significantly higher infusion rates of propofol than men (4.5 *vs* 4.0 mg kg^{-1} h^{-1}, P=0.0002). However, these findings could be explained by a more rapid clearance or distribution of propofol in the females as well as by differences in sensitivity to propofol.

We aimed at keeping the pharmacodynamic effect constant and similar by targeting the propofol infusion to achieve a defined BIS value. The BIS values at both termination of anaesthesia and awakening were similar in the two groups, but the measured propofol levels tended to be higher in the males. This suggests an increased sensitivity to propofol in women. Gender difference in drug sensitivity has previously been shown for other drugs, such as morphine.[20 21]

Our study has limitations. It is generally accepted that a multicompartmental kinetic model, using two[12] or three[13 17] compartments, fits best for propofol. By infusing propofol within a narrow range of targets for 1–2 h and keeping a constant serum target for at least 15 min before the first sample, it is reasonable to assume that, for all practical purposes, the plasma concentration should be stable at that point of time. However, when the infusion is stopped there will be propofol clearance and some ongoing diffusion into poorly circulated tissue, both of which will reduce the plasma concentration. Whereas propofol clearance may be adequately described with a single constant for first-order logarithmic decline, the diffusion into tissue will involve an additional constant although it is also a first-order process. Ideally, several samples of plasma concentration should be used to characterize the different constants precisely. Because of the short time-span for sampling (5–10 min) and inherent limitations in the precision of a blood sample to designate an exact effect site concentration at an exact point of time, we simplified the procedure by using two samples and designating one k value for the decline during the short-time span in question. As the same simplification was performed in both genders after a similar duration

of infusion, comparison between genders should still be valid.

The study is based on venous sampling. Schuttler and Ihmsen[14] showed that venous propofol concentrations are similar to arterial concentrations except during the initial rapid distributional phase. As we have measured concentrations of propofol after a continuous infusion of 1–2 h, it is unlikely that any change in the plasma concentration would be reflected more precisely in arterial samples than in venous samples.

Plasma is not the effect site for propofol, which acts in the central nervous system. There is a certain equilibrium delay between a particular plasma concentration and the corresponding drug effect,[22] which is most apparent after a rapid increase in the blood concentration. The delay is less important when the blood concentration is decreasing after prolonged infusion, because a decrease will be slower, allowing time for the effect site concentration to equilibrate closer to the blood concentration.[23] The delay in the equilibrium is reflected by the k_{eo}. No investigations have been performed to establish whether the k_{eo} for propofol is influenced by gender.

Unfortunately, no method of directly measuring the actual drug concentration at the effect site is available. BIS has been documented as a sensitive parameter of hypnotic propofol effect in the awake–asleep distinction, i.e. BIS values in the range 60–70.[6] There is a similar relationship between BIS and the sedation score in the two genders in this range (Scott Greenwald, Aspect Medical, personal communication). However, at lower levels of BIS, such as the mean value of 45 in our patients, it is more difficult to document correlation between BIS values and different levels of hypnotic effect because of a lack of useful clinical correlates. For this reason we do not know for sure whether a similar BIS of 45 actually represents a similar hypnotic effect in the individual patient.

We intended to keep propofol as the only sedative medication. To ensure analgesia during surgery we used a regional block. It has been suggested that a regional block can influence the degree of sedation,[24] probably because of a less afferent input into the central nervous system.[25] The male and female patients in the present study had a regional block which reached the same mean sensory level (Table 2). We can assume that the eventual contributing sedative effect of the block would be equal in the two groups.

In conclusion, we have demonstrated that a faster decline in plasma propofol is a likely explanation for the faster emergence from propofol anaesthesia repeatedly shown in women. Our study encourages the implementation of gender as a covariate in propofol dosing schemes and computerized delivery systems. It is an open question as to whether a true gender difference in the speed of elimination of propofol exists, or whether the difference in the decline simply reflects differences in intercompartmental distribution factors. There might also be a gender difference in the pharmacodynamic effect of propofol, with women being more sensitive to a given plasma concentration than men.

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