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Extended Abstract
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Pharma Sci 2020-Impact of Gender Variation on Calculated Plasma Concentration of Propofol (Cp50calc) to Prevent Movement Response to Surgical Stimulus in South Indian Population: A Comparative Study-Sri Balaji Vidyapeeth (Deemed to be University), India

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Introduction

Propofol is an intravenous anesthetic agent used since 1980s for the induction and maintenance of anesthesia in day care surgery. It has the unique property of rapid induction with rapid and complete recovery from general anesthesia. Propofol undergoes multicompartmental pharmacokinetics. Hence, continuous measurement of plasma concentration of propofol (Cp) throughout the surgical procedure is a difficult task. Several manual infusion regimens were put forth to optimize the dose requirement and ensure rapid emergence. However, their use was limited by the inaccurate prediction of propofol plasma concentration which was overcome by Marsh et al. They used a three-compartment pharmacokinetic model in comparison to other models with minimal prediction errors.

Preprogrammed computerized target-controlled infusion (TCI) device combines a pharmacokinetic model with an infusion pump and helps an anesthesiologist to titrate target blood propofol concentrations according to the requirement. Diprifusor is a standard computerized TCI device which incorporates the Marsh pharmacokinetic model with an infusion pump and helps to adjust the target plasma propofol concentration or the effect site propofol concentration.

Cp_{calc} of propofol is the predicted plasma concentration of propofol, calculated based on the formula employed in the TCI pumps that incorporates various pharmacokinetic variables such as volume of distribution, clearance, and nonpharmacokinetic variables, namely age, weight, etc., Nonpharmacokinetic factors such as gender and ethnicity do alter the Cp_{calc} of propofol, but there are only very few literary reports and are not considered while administering the propofol infusion with TCI.

$Cp50_{calc}$ of propofol is defined as the calculated plasma concentration of propofol, at which 50% of the patients anesthetized with propofol do not respond to standard surgical stimulus.

More studies are required to conclude the influence of nonpharmacokinetic variables such as age, gender, and geographic differences on the plasma concentration of propofol, so that prediction errors will be minimized in the TCI pumps by incorporating these variables in their software. Hence, we designed this study to determine the gender differences in the Cp50calc of propofol required to prevent movement response to surgical stimulus, particularly in the South Indian population.

Materials and Methods

After approval by the Institutional Research and Human Ethics Committee, a comparative observational study was performed on unpremedicated thirty male and thirty female patients, aged 20–50 years, American Society of Anesthesiologists (ASA) Physical Status Grade I and II, and scheduled for elective minor day care surgery under general anesthesia over a study period of 1 year. A thorough preoperative checkup was done and written informed consent obtained from all the patients during the study period. Patients posted for emergency surgeries, propofol hypersensitivity, pregnant patients, and chronic alcoholics were excluded from the study.

On arrival in the operative room, an 18G intravenous cannula was secured in the forearm vein and ringer lactate solution was administered as 10 ml/kg bolus followed by 10 ml/kg/h. First patient of each group

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received a fixed intravenous bolus dose of 1.5 mg/kg of propofol (Profol, Claris Life Sciences Limited, Ahmedabad, Gujarat, India) over 2 min followed by continuous infusion of 150 μg/kg/min over next 10 min (B Braun Syringe Perfusor, Pennsylvania, USA). This was the minimal maintenance dose required to produce the desired therapeutic effect based on previous studies. Patients received 100% oxygen during propofol infusion by breathing circuit. No other anesthetics were administered during this period. At the end of 10 min, a small skin incision was made at the operative site. Presence or absence of movement response to skin incision was noted by the surgeon who was blinded to the dosage and anesthesia was deepened as per the anesthesiologist's choice and the surgery commenced. Movement response was defined as gross purposeful movement of head or extremities as per Eger et al.

Dixon's up-and-down method

The maintenance dose of the next patient in each group was determined by the presence or absence of movement of the present study patient. This method followed was same as that of up-and-down sequential allocation by Dixon and Mood. If the patient moved, the maintenance infusion rate was increased by 10 μg/kg/min for the next patient. If there was no movement, the maintenance infusion rate was reduced by 10 μg/kg/min for the next patient. This stepping dose of 10 μg/kg/min approximates the standard deviation based on previous studies. There was no change in bolus dose of propofol used for induction of anesthesia. Hemodynamic parameters were recorded preoperatively, during induction, and at skin incision. The weight, age, and propofol dose was fed to the pharmacokinetic formula used in the Rugloop II propofol calculation validation Excel Spreadsheet based on Marsh pharmacokinetic model for each patient in each group and the plasma concentration of propofol (Cpcalc) for each patient was calculated. All statistical data were recorded and analyzed using Microsoft excel.

The study was concluded when three consecutive crossovers from movement-to-no movement response to skin incision was obtained.

Sample size in each group was determined by Dixon's method, where in three consecutive crossovers from movement-to-no movement response to surgical stimulus was sufficient enough to reach steady-state plasma propofol concentration. Asum of thirty patients in each group were sufficient enough to manifest three consecutive crossovers in our study. Consecutive sampling technique was carried out in each group to step up or step down the maintenance dose.

$Cp50_{calc}$ of propofol

$Cp50_{calc}$ of propofol required to prevent movement response was determined by calculating the mean concentration of all independent pair of patients who manifested a consecutive crossover from movement-to-no movement response at steady state.

Results

The demographical profile and the hemodynamic parameters measured preoperatively, but clinically insignificant. There was no significant difference in the calculated plasma propofol concentration between males and females following an intravenous bolus dose. Cp_{calc} of propofol required to prevent movement response to skin incision following a maintenance infusion of propofol was determined by calculating the mean concentration of all independent pair of patients who manifested a consecutive crossover from movement-to-no movement response at steady state and gender differences were compared.

$Cp50_{calc}$ of propofol

$Cp50_{calc}$ of propofol required to prevent movement response to surgical stimuli in 50% of the patients was found to be 6.336 + 0.149 μg/ml in males and 5.664 + 0.149 μg/ml in females. Thereby, the dose range of propofol required to prevent movement in 50% of the patients was calculated to be 320–330 μg/kg/min in males and 290–300 μg/kg/min in females.

Discussion

Gender is an important variable that can alter the pharmacokinetics and pharmacodynamics of drugs, anesthetic drugs in particular.[18] There are numerous

studies that quote gender differences in pharmacokinetics and can be easily determined by measuring the plasma drug concentration. The clinical significance and the reality of gender differences in drug effects can be made only if the pharmacokinetic variables are measured along with the clinical outcome. Our study measured the Cp50calc of propofol to prevent movement response to surgical stimulus and compared the gender differences.

Propofol is a lipid-soluble drug undergoing multicompartmental pharmacokinetics and has a high hepatic extraction ratio.[3] Pleym et al. mentioned in this review that there is increased body fat and reduced body water in females.[18] Accordingly, the volume of distribution (defined as the ratio of plasma drug concentration to the amount of drug in the body called Vd) may vary with sex. Moreover, Vd for lipid-soluble drugs like propofol is higher in females than males, and this is reflected as lowered initial plasma concentration in females.

Therefore, drug dosage calculated on the basis of body weight can affect the plasma drug concentration and also attribute to the gender differences where females have high Vd and higher body fat. In this study, there was no significant difference found in the calculated plasma propofol concentration between males and females following an intravenous bolus dose. This plasma concentration following bolus dose can vary and steady-state plasma concentration is achieved following infusion. Vd does not have a major influence on steady state, but clearance plays a major role. Therefore, hepatic metabolism, the major route of propofol elimination can cause gender differences in dose requirement.[19]

In our study, the calculated plasma concentration of propofol (Cp50calc) to prevent movement response to surgical stimulus was 6.336 + 0.149 µg/ml in males and 5.664 + 0.149 µg/ml in females. The metabolism of propofol is dependent on hepatic blood flow and has a high hepatic extraction ratio. Since the cardiac output and total liver blood flow is lesser in females, it may be one of the probable reasons for less propofol dose requirement in females to achieve steady state in our study.

Moreover, propofol undergoes glucuronide conjugation[20] by UGT1A9 enzyme to form propofol glucuronide and hydroxylation by cytochrome P450 enzymes, namely, CYP2B6 and CYP2C9 to form 4-hydroxy propofol. Hence, genetic polymorphisms in CYP2B6 and CYP2C9 can also account for the gender differences. Choong et al. [21] evaluated the gender differences in propofol metabolite formation and reported that metabolite formation was higher in females compared to males, since the estrogen receptors have an increased expression of CYP2B6 gene. Hence, propofol is metabolized faster and may probably account for the lowered Cp50calc of propofol in females in our study. Similar to our study, Kodaka et al. studied the effect of anesthetic requirement for loss of consciousness (LOC50) using sevoflurane or propofol in Chinese population on 150 unpremedicated, 18–40 years, ASA I–II patients by Dixon up-and-down method.[22] No statistically significant difference was seen with sevoflurane, whereas men required 2.9 ± 0.2 µg/ml of propofol and found to be significantly more than women (2.7 ± 0.1 µg/ml).

The higher plasma concentration in both sexes found in our study may also be due to the ethnic differences or to the use of propofol alone for induction without use of other anesthetics like sevoflurane. Moreover, the study was conducted on unpremedicated patients who will require higher dose of propofol for sedation. A study by Oku et al. on Cp50 for propofol for total intravenous anesthesia in animal studies also report higher values of 5.3 ± 1.4 µg/ml after xylazine premedication in horses.[23]

Natarajan et al. conducted a study on 50 White and 50 Black patients aged 18–65 years compared the propofol dose causing loss of verbal response and suppression of Bispectral Index to 50.[24] Propofol was infused at 40 mg/kg/h and reduced to 8 mg/kg/h when the Bispectral Index fell to 50. A statistician, blinded to patient ethnicity, found that the mean propofol dose for loss of verbal response in White patients was 1.41 mg/kg and 1.16 mg/kg in Black patients ($P < 0.001$). The dose of propofol required for loss of verbal response, was lower in Black than in White patients. He stated that polymorphisms in genes

coding for the central nervous system receptors that respond to propofol, such as gamma aminobutyric acid receptor subunits, might contribute to ethnic variations in propofol susceptibility. In our study, response to skin incision was the clinical outcome assessed, which needs deeper sedation, hence higher concentration of propofol needed. Moreover, studies on the ethnic differences in propofol dose and concentration have not been reported in our population.

The limitation of our study was that, we measured the calculated plasma concentration of propofol using the Marsh pharmacokinetic model and not the actual plasma propofol concentration.

Conclusion

Differences in nonpharmacokinetic variables like gender do alter the Cpcalc of propofol as revealed by our study, but the precise mechanism for the gender differences in the dose requirement of propofol is not established. Moreover, the available evidence supporting the clinical impact of the patient's gender on propofol dose requirement is quite conflicting. Hence, further research in this area is required to clarify this issue so that the TCI pumps that incorporate different pharmacokinetic models can incorporate gender variations too in their software in order to further personalize drug dosage.

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Conflicts of interest

There are no conflicts of interest.

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