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Hypnotic and cardiovascular effects of proprietary and generic propofol formulations do not differ

Purpose: The aim of the study was to compare the potency of two different propofol formulations: proprietary and generic propofol using the bispectral index (BIS) monitoring.

Methods: Forty female patients undergoing breast surgery received propofol 3 mg·kg⁻¹ followed by propofol infusion adjusted to maintain a 40% BIS value, supplemented by 50% nitrous oxide. Proprietary or generic propofol was administered in a randomized double-blind manner.

Results: The propofol mg/BIS% ratio obtained after the bolus dose, the cumulative infused propofol mg/BIS% ratio at the end of each five-minute interval and the total dose of propofol administered as bolus + infusion were similar between the two groups. The two groups did not differ with regard to systolic and diastolic blood pressure, heart rate, end-tidal carbon dioxide and arterial oxygen saturation.

Conclusion: The two propofol formulations are equipotent when hypnotic effect is assessed by BIS monitoring.

Objectif : Comparer l'efficacité de deux formulations différentes de propofol, le propofol de marque déposée et le propofol générique, à l'aide du monitoring de l'index bispectral (BIS).

Méthode : Quarante patientes devant subir une opération mammaire ont reçu 3 mg·kg⁻¹ de propofol suivis d'une perfusion de propofol, adaptée pour maintenir une valeur BIS à 40 %, complétée par du protoxyde d'azote à 50 %. Le propofol breveté ou générique a été administré de façon aléatoire et à double insu.

Résultats : Le ratio mg de propofol/%BIS obtenu après l'administration du bolus, le ratio cumulatif mg de propofol/%BIS perfusé à la fin de chaque intervalle de cinq minutes et la dose totale de propofol administré sous forme de bolus + perfusion ont été similaires dans les deux groupes. La tension artérielle systolique et diastolique, la fréquence cardiaque, le gaz carbonique de fin d'expiration et la satu-

ration du sang artériel en oxygène n'ont pas présenté de différence intergroupe.

Conclusion : Les deux formulations de propofol sont équivalentes comme le démontre l'évaluation de l'effet hypnotique par le monitoring BIS.

DIPRIVAN® (AstraZeneca, Sweden), is an oil-in-water emulsion, which contains soybean oil and purified egg phosphatide. Propofol is dissolved in the oil phase of the emulsion, which is dispersed to submicron size in the aqueous phase giving a stable product. Propofol prepared by Abbott Laboratories, using the same solvent, has become available recently. The present study compares the hypnotic potency using the Bispectral Index™ (BIS) and the hemodynamics of the 1% propofol manufactured by AstraZeneca (proprietary) and that manufactured by Abbott Laboratories (generic).

Methods

The study was approved by the Hospital Ethics Committee and patients gave written informed consent to participate. Forty female patients ASA physical status I scheduled for excision of breast mass were assigned randomly to receive proprietary or generic propofol. Patient randomization and preparation of propofol infusion were carried out by an independent investigator. Anesthesiologists and patients were blinded to the formulation administered. Patients weighing more than 20% of their ideal body weight, or receiving sedatives, analgesics, or hypnotics, were excluded.

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In the operating room, a 17-gauge catheter was inserted in a peripheral vein for the bolus and subsequent infusion of propofol. The electroencephalogram (EEG) signal was obtained from Zipprep™ electrodes (Aspect Medical System, MA, USA) applied to the forehead and temple using a frontal-temporal montage. The real-time EEG and BIS were continuously displayed on an EEG monitor (Bispectral Index™, software version 3.66.24, Spacelabs Medical, Redmond, WA, USA).

After preoxygenation, patients received a bolus dose of *iv* propofol $3 \text{ mg} \cdot \text{kg}^{-1}$ and rocuronium $0.6 \text{ mg} \cdot \text{kg}^{-1}$. Anesthesia was maintained with 50% nitrous oxide in oxygen and a continuous propofol infusion titrated to maintain a BIS of 40%. Blood pressure, heart rate, peripheral oxygen saturation, end-tidal carbon dioxide and BIS values were recorded at five-minute intervals. Propofol volume delivered, BIS% and hemodynamic parameters were recorded for 30 min.

The cumulative propofol infusion per kg body weight delivered every five minutes was normalized per BIS% unit, by dividing the dose of propofol infused at each predetermined time interval by the BIS value corresponding to the end of the same interval. The same calculations apply to the bolus doses of propofol administered to induce anesthesia. To obtain numbers greater than one, all the propofol (mg)/BIS% ratios were multiplied by 100.

Statistical analysis was performed with the SPSS 8.0 package. From an initial estimate of the dose of propofol/kg body weight infused in 30 min ($4 \text{ mg} \cdot \text{kg}^{-1}$) and the standard deviation (0.8), we concluded that our study would have sufficient power (>80%) to detect a 20% difference between the two groups with more than 15 patients in each group. Age and body mass index were compared with Student's *t* test. Mean arterial pressure (MAP), heart rate, peripheral oxygen saturation, end-tidal carbon dioxide, BIS values and propofol normalized for the obtained BIS values were compared by the repeated measures general linear model procedures.

Results

The two groups that received the proprietary or generic formulation of propofol were similar with regard to age (mean and SD values 39 ± 7.3 and 42 ± 6.1 yr) and body mass index (23 ± 3.7 and 25 ± 2.7).

No difference was found in the BIS values between the two groups at any time interval (Figure 1). The BIS values recorded after the bolus induction dose were lower compared to the ten, 15, 20, 25 and 30 min recordings ($P < 0.001$) in both groups. The dose of propofol infused after each time interval did not

FIGURE 1 Mean values (SD) of BIS for the proprietary and generic propofol formulations before intubation and at five-minute intervals for a period of 30 min.

FIGURE 2 Mean values (SD) of propofol ($\text{mg} \cdot \text{kg}^{-1}$) administered as a bolus and a cumulative infusion normalized for the BIS% values in the groups that received the proprietary or generic propofol.

differ between the two groups, nor did the dose of propofol infused per kg body weight and normalized for the corresponding BIS value (Figure 2).

Heart rate recorded five minutes after tracheal intubation was higher than at any other time ($P < 0.01$ for all pair comparisons). Changes in heart rate were not different between groups ($P = 0.35$). Preoperatively, MAP differed between groups (difference between mean values 7.7 mmHg , $P = 0.05$). During the study, MAP differed statistically between and within the two groups ($P < 0.01$ and $P < 0.01$ respectively). The maximum difference was approximately 10 mmHg . Changes in MAP were not different between groups ($P = 0.37$).

Discussion

Our results show no difference between proprietary and generic propofol regarding potency, as determined by titrating the propofol infusion to obtain a 40% BIS. The changes in hemodynamic parameters were also similar in the two groups. Although a difference in MAP was observed between groups, this difference was small and of little clinical significance.

In the present study we used BIS, as the endpoint of hypnosis to control the administration of propofol and to assess the potency of the two different propofol formulations. BIS was developed from a database of EEG segments, which correlated well with the hypnotic and sedation levels in volunteers given increasing and decreasing doses of several anesthetics.^{1,2} BIS has been used to monitor propofol-induced sedation and anesthesia. Endpoints for induction of anesthesia during propofol infusion with or without fentanyl were compared with BIS values.³ The impact of alfentanil on propofol requirements for loss of consciousness and lack of recall was also assessed using the BIS monitoring.⁴

The propofol (3 mg·kg⁻¹)/BIS ratio and, thus, the hypnotic effect obtained after the predetermined bolus dose did not differ between groups. The cumulative infusion doses required to maintain a BIS 40% normalized by the corresponding BIS values did not differ between the two groups as well. As BIS is not altered by nitrous oxide,⁵ this agent was chosen to provide intraoperative analgesia for a procedure which is not associated with severe pain.

We chose a 40% BIS value as the anesthetic endpoint because no awareness has been described in the literature with a BIS less than 50%.⁶ BIS values correlate well with the hypnotic level produced by general anesthetics but not with the hemodynamic changes associated with endotracheal intubation and sternotomy.⁷ Since BIS does not predict equally effectively the somatic and autonomic responses, our results concerning the equipotency of the two propofol formulations studied apply to sedation alone.

In summary, the two propofol formulations (proprietary and generic) compared by BIS monitoring were similar with regard to their hypnotic and hemodynamic effects.

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