Comparison of Proprietary and 3 Generic Formulation of Propofol for Induction of General Anesthesia –

Cyrus Motamed*, Veronique Delcour, Jean Pierre Laventure and Valerie Billard

Department of anaesthesia at Gustave Roussy Institute, Villejuif, France

*Address for Correspondence: Cyrus Motamed, Department of anaesthesia at Gustave Roussy Institute, Villejuif Cedex, France, E-mail: Cyrus.MOTAMED@guslaveroussy.fr

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INTRODUCTION

Propofol (2.6 di-iso-propyl-phenol), lipid-soluble, non-barbiturate intravenous hypnotic drug available since 1986, is the first IV anesthetics used in the world for induction of general anaesthesia with a recommended ED$_{95}$ of 2.5 mg.kg$^{-1}$ [1]. It is well tolerated but may show minor side effects as pain on injection, rash or myoclonies [1].

At the time of the study several generic propofol formulations were available in our country, combined or not with antibacterial preservatives, according to each country regulatory requirements.

Four propofol formulations, all preservative-free, were available: Diprivan’ (Astra Zeneca) and 3 generic propofol. They are assumed to be bioequivalent in efficacy but may differ regarding side effects due to specific solvent composition and chemical properties. Thus, the choice of a formulation based on cost considerations is ethically acceptable only when products are equally efficient and their side effects such as Pain on Injection (POI) could be considered as clinically minor or similar between formulations.

Whereas Diprivan’ and Propofol Lipuro’ have been extensively compared, few clinical data are available comparing at least 3 formulations [2].

The aim of this study was to describe simultaneously efficacy features and immediate side effects of the propofol bolus for induction at the time of the study in France, given as a slow IV bolus for induction of general anaesthesia.

METHODS

The study was approved by our local Institutional Review Board at Gustave Roussy Institute. Since all study medications were available in France and no change of practice was done, written informed consent was waived as there was no element opposing any ethical considerations and the rights of patients were respected according to Helsinki convention. Patients undergoing surgery under general anaesthesia, having no expected difficult intubation, no need for a rapid sequence induction technique (full stomach, gastro-oesophageal reflex, morbidly obese…) and no central venous catheter were prospectively included. After informed consent patients received randomly for induction one of the 4 preservative-free propofol formulations available at the time of the study in France: Propofol® Fresenius (Fresenius Kabi), Propofol Dakota Pharm’, Propofol Lipuro® (B. Braun Medical) or Diprivan’ (Astra-Zeneca). The anaesthesiologists in charge and the patient were blinded to the formulation chosen which was prepared by another nurse anaesthetist. All patients were pre-medicated with hydroxyzine (1-1.5 mg.kg$^{-1}$ 2 hours before induction). In the operating room, a peripheral venous catheter 18 or 20G was inserted on the dorsum of the hand or forearm. Monitoring of electrocardiogram, non-invasive blood pressure and pulse oximetry were installed using Datex Ohmeda’ anesthesia machine.

Patients received an intravenous bolus of sufentanil (0.2 μg.kg$^{-1}$). Then, after 3 minutes, propofol 1% was manually injected at the rate of 5 mg.sec$^{-1}$ (0.5 ml every sec) until loss of eyelash reflex and easy face mask ventilation. When surgery required orotracheal intubation, it was performed 3 minutes after a bolus of atracurium 0.5 mg.kg$^{-1}$ given intravenously after loss of consciousness. Otherwise, airway was controlled by a Laryngeal Mask (LMA).

Efficacy of the propofol bolus was assessed by:
- the onset time and propofol dose required for Loss of Eyelash Reflex (L.E.R.)
- jaw relaxation after loss of consciousness (good or poor)
- face mask ventilation (easy or difficult) and motor response to mandibular luxation
- laryngeal mask insertion conditions (easy, difficult or failed, cough or not).

When orotracheal intubation was performed, intubation conditions were not analysed since all patients had received a non-depolarizing neuromuscular blocking drug, which is known to be the main factor influencing intubation conditions.

Side effects of the propofol bolus were expressed using the following items:
- Pain on injection, elicited with questioning and scored as none, mild or severe.
RESULTS

Over a 2 months period, from January to March 2010, 146 patients were included in this study and received randomly either Propofol® Fresenius (n = 35), Propofol Dakota Pharm® (n = 33), Propofol Lipuro® (n = 40) or Diprivan® (n = 38). There was no difference in induction events. Statistical analysis compared efficacy and side effects between propofol formulations using a Chi-2 test for binary variables and ANOVA for quantitative variables. A threshold \( p < 0.05 \) was considered statistically significant.

Efficacy

In all patients, unconsciousness was achieved and face mask ventilation was possible, although it was judged as "uneasy" in 11 patients, with a poor jaw relaxation in 10 patients, and 26 patients had a transient motor response to mandibular luxation. No difference related to the propofol formulation could be demonstrated neither in induction dose, induction time, and face mask ventilation nor in LMA insertion conditions (table 2).

Side effects

Eighty one patients (55%) complained of pain during induction, mild for 54 of them (37%) and severe for the 27 others (18%), without reaching statistically significant difference between the 4 groups (table 3).

Among the 81 patients who signalled pain during induction, only half of them remembered it after recovery, similarly for all formulations. Among the 65 patients who did not complain during induction, 4 of them answered after recovery that they did remember some pain related to propofol injection, 2 having received propofol Lipuro® and 2 after Diprivan®.

A forearm rash was observed in 10 patients (7%) and myoclonies in 7 patients (5%) without any statistically significant difference related to the propofol formulation (table 3). No clinically relevant consequence of these side effects was observed.

Discussion

Since the release of Diprivan® almost 35 years ago, propofol has become the most commonly used drug of choice for anaesthesia induction, maintenance and sedation in ICU patients.

Because it is not water soluble, propofol must be prepared in fat emulsions. Diprivan® uses a 10% soybean oil-based emulsion composed of long-chain triglycerides. Generic formulations, have slightly modified solvent composition. Propofol Lipuro® is diluted in a mixture (1:1) of medium and long-chain triglycerides whereas Fresenius and Dakota Pharm formulations contained only long chain triglycerides but had a slightly different 10% soybean oil composition to reinforce emulsion stability.

However, modifying the solvent may impair physico-chemical properties and theoretically influence pharmacokinetic, pharmacodynamics or side effects of the formulation.

First, it may increase the free propofol content in the emulsion [3,4], which may increase propofol diffusion to the lungs and decrease peak plasma concentration as observed in rats [5]. It may also delay the transfer to the CNS, and modify pharmacodynamic properties as induction dose, onset or EEG effects [6].

Such influence was not observed in our study neither on induction doses nor on onset times or ease of airway management. It was not observed either in clinical studies comparing pharmacokinetics or pharmacodynamics of various propofol formulations [6-13].

These results suggest that the difference in free propofol concentration between formulations was not big enough (free propofol 14 μg.ml⁻¹ in Propofol Lipuro® vs. 19.76 μg/mL in Diprivan® or 19.42 μg.mL⁻¹ in Propofol® Fresenius [14] to have a clinically relevant effect on propofol pharmacokinetics or dynamics, which is an expected result from a generic formulation of a drug. However, kinetics and dynamics of formulations should be re-examined for long duration infusion where distribution phenomenon achieved steady state.

The second issue raised by changing the solvent composition is...
the incidence of side effects as pain on injection. Pain on injection is indeed a critical issue during propofol induction, it has been extensively studied with at least 177 trials that randomised more than 25,000 adults [15], since it has been observed in 20 to 70% of the patients [16,17], and has been qualified as severe in 10 to 33% [7,18].

It can be reduced by a third to a half when using a LCT/MCT solvent [7,18]. The main mechanism incriminated is again the free propofol content or slow rate of injection [19]. The high incidence of pain observed with Propofol Lipuro 2% (same medium-long chain triglyceride but more free propofol than Propofol Lipuro 1%) [8] with ampropol (half soybean concentration vs. Diprivan’) [11] or with AM149 (no soy bean, pure medium chain triglycerides mixture but high free propofol content) [16], supports this hypothesis.

Our results were in a similar range than published studies (severe pain in 32% of the patients with Diprivan, 15% with Fresenius, 17% with Dakota Pharm, and 10% with Propofol Lipuro) but failed to demonstrate a statistically significant difference between formulations. This lack of statistical significance may be due to the number of groups compared (4 groups) which decreased the statistical power of the study. But it can also suggest that no propofol formulation could completely suppress pain on injection and that other mean to prevent pain should be recommended anyway.

Many recipes have been proposed for this purpose, as cooling,

<table>
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REFERENCES


