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Research Article

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

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ABSTRACT

Background: This study compared the properties of propofol bolus for induction of general anaesthesia between proprietary and 3 generic formulations, to assess if solvent differences had clinically relevant consequences on efficacy or side effects. Many studies have investigated different formulations of propofol for side effects, in this study we also focused on efficacy of different formulations for induction of general anaesthesia.

Methods: 146 patients scheduled for general anaesthesia received for induction one of the propofol formulations available in our country i.e. 35 had Propofol® Fresenius, 33 Propofol Dakota Pharm®, 40 Propofol Lipuro®, 38 Diprivan® injected in a peripheral venous catheter, and preceded by sufentanil 0.2 µg.kg⁻¹. Airway control was based on intubation (n = 90, facilitated by atracurium), or laryngeal mask (n = 56).

Efficacy was assessed by induction dose, ease of face mask ventilation and airway device insertion. Pain on injection, rash, or myoclonies were recorded as side effects.

Propofol formulations were compared by Anova or Chi 2 test.

Results: Expected hypnotic effects propofol injection were similar in the 4 groups, satisfying and consistent with previous publications.

Pain on injection was present in 55% of patients (n = 81), mild in 36% (n = 54), and severe in 18% (n = 27). Myoclonies occurred in 4% of patients (n = 7) and local rash in 6% of patients (n = 10). Differences between formulations did not reach statistical significance.

Conclusion: The propofol formulations tested appeared similar on efficacy, with minor differences regarding side effects. No formulation could suppress totally pain on injection and associated treatment as lidocaine should be widely used.

Keywords: Pain with propofol; Pain on propofol injection; Propofol adverse effects

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 ED₉₅ 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 (POPI) 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 formulations available 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 scheduled surgery under general anaesthesia, having no expected difficult intubation, no need for a rapid sequence induction technique (full stomach, gastro-oesophageal reflux, 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 1% formulations available at the time of the study in France: Propofol® Fresenius (Fresenius Kabi), Propofol Dakota Pharm® (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® anaesthesia 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.

- Other side effects as rash along the injected vein or myoclonies were recorded
- In the recovery room, patients were asked if they had any remembering of pain during injection by a nurse blinded to the induction events.

Results are expressed as mean \pm standard deviation (for demographics, doses and delays) and number of patients (for incidence of 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.

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 between groups regarding weight, height, age, gender and number of patients intubated vs. LMA (Table 1).

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 on injection, 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.

Table 1: Patient's description. Results are expressed as Mean \pm SD or number of patients. None of the items displayed differed significantly between propofol for mulation.

Propofol formulation	Fresenius	Dakota Pharm	B.Braun Medical	AstraZeneca
Number of patients	35	33	40	38
Weight (kg)	64 \pm 14	65 \pm 14	69 \pm 12	68 \pm 14
Height (cm)	164 \pm 9	166 \pm 9	164 \pm 7	164 \pm 8
Age (yr)	54 \pm 14	51 \pm 15	54 \pm 14	55 \pm 12
Sex (F / M)	28 / 7	24 / 9	35 / 5	32 / 6
Airway control Laryngeal mask	14	9	20	13
Intubation	21	24	20	25

Table 2: Efficacy of propofol formulations given at a rate of 5 mg.sec⁻¹ for induction. Results are expressed as Mean \pm SD or number of patients. None of the items displayed differed significantly between propofol formulations.

Propofol formulation	Fresenius	Dakota Pharm	B. Braun Medical	AstraZeneca
Number of patients	35	33	40	38
Dose to L.E.R. (mg kg ⁻¹)	2.6 \pm 0.8	2.5 \pm 0.7	2.4 \pm 0.4	2.5 \pm 0.7
Onset time to L.E.R. (min.)	1.2 \pm 0.9	1.0 \pm 0.3	0.9 \pm 0.4	1.1 \pm 0.5
Poor jaws relaxation (n =)	4	2	0	4
Uneasy face mask ventilation (n =)	4	1	4	2
Response to mandibular luxation (n =)	7	9	5	5
Laryngeal mask insertion				
Number of patients	14	9	20	13
Delay from induction (min.)	2.5 \pm 1.3	3.3 \pm 1.3	1.9 \pm 0.6	2.3 \pm 1.1
Insertion difficult (n =)	4	2	2	1
Cough after inserting (n =)	3	0	1	0

L.E.R: Loss of Eyelash Reflex.

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 $\mu\text{g}\cdot\text{mL}^{-1}$ in Propofol Lipuro[®] vs. 19.76 $\mu\text{g}/\text{mL}$ in Diprivan or 19.42 $\mu\text{g}\cdot\text{mL}^{-1}$ 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 ampophol (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 3: Side effects of a slow propofol bolus (5 mg.sec⁻¹) expressed by the number of patients having complained of pain on injection, or having shown local rash or myoclonies. None of the items differed significantly between propofol formulations.

Propofol formulation	Fresenius	Dakota	Lipuro	Astra-Zeneca
Number of patients	35	33	40	38
Pain on injection				
No	17	10	21	17
Mild	12	18	15	9
Intense	6	5	4	12
Myoclonies	2	1	3	1
Forearm rash	5	3	2	0

filtering or diluting propofol, adding magnesium (which induced pain by itself!), ephedrine, metoprolol, butorphanol, ketamine, thiopentone or gabapentin [19-22].

The most efficient and simple technique to decrease pain on propofol injection is probably intravenous lidocaine (20 to 40 mg), when administered 30 to 120 sec prior to propofol with a tourniquet [21]. Lidocaine mixed in the propofol has also been proposed [4,23-29] and may be more efficient than an IV. bolus given before propofol [30]. In this case, propofol-lidocaine mixture should imperatively be prepared immediately before use to avoid both emulsion destabilization developing over time [31,32] and bacterial growth [33]. Currently data from RCTs confirm that both lidocaine admixture and pre-treatment are effective in reducing pain on propofol injection and there were no significant differences of effect between the two techniques [20,34] In another recent study Granisetron as pretreatment has been found to be more efficient than lidocaine [35]. Intravenous opioids may also reduce the incidence of pain [21,27], but failed to suppress it totally, as observed in our study where patients had received sufentanil.

Out of pain on injection [36] which might not be considered as important by patients themselves [37] other side effects are rarely mentioned in literature. Local erythema was noted by Paul M et al. with AM149 (no soybean oil, MCT), but not with diprivan [16], and no interpretation was attempted. After we have estimated their incidence between 5 and 15 %, further studies may examine the influence of premedication, lidocaine on myoclonies or rash [24].

We conclude that the four propofol formulations available at the time of the study were considered as equivalent in their efficacy to induce general anaesthesia in adults (it should be added that propofol Dakota is no more available In France). Mild differences in side effects do exist: pain on injection can be reduced but not suppressed by modifying the solvent, suggesting that other means for preventing pain (choice of a large vein, lidocaine ± opioid) should always be recommended. Other side effects as rash or myoclonies should be further studied to be understood and prevented. The side effects observed were not relevant criteria to choose between formulation. This choice may therefore be supported by economic considerations.

Appendix: Details of different formulations of propofol:

Diprivan	Propofol Dakota Pharm	Propofol Fresenius	Propofol Lipuro 1%
<ul style="list-style-type: none"> Soya oil (notorious effect) Purified Phosphatid of egg Glycerol (E422) Disodium Edetat (E385) Sodium hydroxyde (E524) Water for injectable preparations. Présence of Sodium (notorious effect) 	<ul style="list-style-type: none"> Soya oil (notorious effect) Purified Egg lecithin Glycerol (E422) Oleic acid Sodium hydroxyde (E524) Water for injectable preparations 	<ul style="list-style-type: none"> Refined soya oil (notorious effect) (100 mg) Purified egg lecithin Glycerol (E422) Oleic acid Sodium hydroxyde (E524) 0.06 mg max Water for injectable preparations 	<ul style="list-style-type: none"> Soya oil (notorious effect) Glycerol (E422) Triglycerides with medium chain Egg lecithin Sodium oleate Water for injectable preparations

REFERENCES

- Cummings GC, Dixon J, Kay NH, Windsor JP, Major E, Morgan M, et al. Dose requirements of ICI 35,868 (propofol, 'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia*. 1984; 39: 1168-1171. <https://doi.org/10.1093/aes/39.8.1168>
- Beyaz SG, A TF, Tokgoz O. The effect of propofol lipuro with and without lidocaine on injection pain in children. *Niger J Clin Pract*. 2011; 14: 60-64. <https://doi.org/10.4103/1119-7443.86444>
- Klement W, Arndt JO. Pain on injection of propofol: effects of concentration and diluent. *Br J Anaesth*. 1991; 67: 281-284. <https://doi.org/10.1093/bja/67.3.281>
- Kam E, Abdul Latif MS, McCluskey A. Comparison of Propofol-Lipuro with propofol mixed with lidocaine 10 mg on propofol injection pain. *Anaesthesia*. 2004; 59: 1167-1169. <https://doi.org/10.1093/aes/59.11.1167>
- Dutta S, Ebling WF. Formulation-dependent brain and lung distribution kinetics of propofol in rats. *Anesthesiology*. 1998; 89: 678-685. <https://doi.org/10.1097/00000612-199809000-00014>



6. Ward DS, Norton JR, Guivarch PH, Litman RS, Bailey PL. Pharmacodynamics and pharmacokinetics of propofol in a medium-chain triglyceride emulsion. *Anesthesiology*. 2002; 97: 1401-1408. <https://goo.gl/yN39Rb>
7. Doenicke AW, Roizen MF, Rau J, Kellermann W, Babl J. Reducing pain during propofol injection: the role of the solvent. *Anesth Analg*. 1996; 82: 472-474. <https://goo.gl/ScPr9f>
8. Egan TD, Kern SE, Johnson KB, Pace NL. The pharmacokinetics and pharmacodynamics of propofol in a modified cyclodextrin formulation (Captisol) versus propofol in a lipid formulation (Diprivan): an electroencephalographic and hemodynamic study in a porcine model. *Anesth Analg*. 2003; 97: 72-79. <https://goo.gl/skzRtj>
9. Pessenbacher K, Gutmann A, Eggenreich U, Gschanes A, Rehak P, List WF. Two propofol formulations are equivalent in small children aged 1 month to 3 years. *Acta Anaesthesiol Scand*. 2002; 46: 257-263. <https://goo.gl/9VfQLH>
10. Cox EH, Knibbe CA, Koster VS, Langemeijer MW, Tukker EE, Lange R, et al. Influence of different fat emulsion-based intravenous formulations on the pharmacokinetics and pharmacodynamics of propofol. *Pharm Res*. 1998; 15: 442-448. <https://goo.gl/Gg2AEw>
11. Song D, Hamza MA, White PF, Byerly SI, Jones SB, Macaluso AD. Comparison of a lower-lipid propofol emulsion with the standard emulsion for sedation during monitored anesthesia care. *Anesthesiology*. 2004; 100: 1072-1075. <https://goo.gl/Cm4Hhd>
12. Ihmsen H, Jeleazcov C, Schuttler J, Schwilden H, Bremer F. Accuracy of target-controlled infusion (TCI) with 2 different propofol formulations. *Anaesthesist*. 2004; 53: 937-943. <https://goo.gl/sfJEDJ>
13. Lee SH, Ghim JL, Song MH, Choi HG, Choi BM, Lee HM, et al. Pharmacokinetics and pharmacodynamics of a new reformulated microemulsion and the long-chain triglyceride emulsion of propofol in beagle dogs. *Br J Pharmacol*. 2009; 158: 1982-1995. <https://goo.gl/yEQiLd>
14. Muller RH. *European Hospital Pharmacy*. 2000; 90: 24-31.
15. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ*. 2011; 342: 1110. <https://goo.gl/5AAaZh>
16. Paul M, Dueck M, Kampe S, Fruendt H, Kasper SM. Pharmacological characteristics and side effects of a new galenic formulation of propofol without soyabean oil. *Anaesthesia*. 2003; 58: 1056-1062. <https://goo.gl/DGxacR>
17. Doenicke AW, Roizen MF, Rau J, O'Connor M, Kugler J, Klotz U, et al. Pharmacokinetics and pharmacodynamics of propofol in a new solvent. *Anesth Analg*. 1997; 85: 1399-1403. <https://goo.gl/RRDCty>
18. Rau J, Roizen MF, Doenicke AW, O'Connor MF, Strohschneider U. Propofol in an emulsion of long- and medium-chain triglycerides: the effect on pain. *Anesth Analg*. 2001; 93: 382-384. <https://goo.gl/LWih3z>
19. Scott RP, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia*. 1988; 43: 492-494. <https://goo.gl/652X3p>
20. Desousa KA. Pain on propofol injection: Causes and remedies. *Indian J Pharmacol*. 2016; 48: 617-623. <https://goo.gl/mepSVZ>
21. Picard P, Tramer MR. Prevention of pain on injection with propofol: a quantitative systematic review. *Anesth Analg*. 2000; 90: 963-969. <https://goo.gl/nimx25>
22. Cakirgoz MY, Demirel I, Duran E, Ozer AB, Turkmen UA, Ersoy A, et al. Gabapentin pretreatment for propofol and rocuronium injection pain: A randomized, double-blind, placebo-controlled study. *Niger J Clin Pract*. 2018; 21: 43-48. <https://goo.gl/RNKe31>
23. Eriksson M, Englesson S, Niklasson F, Hartvig P. Effect of lignocaine and pH on propofol-induced pain. *Br J Anaesth*. 1997; 78: 502-506. <https://goo.gl/qo66mc>
24. King SY, Davis FM, Wells JE, Murchison DJ, Pryor PJ. Lidocaine for the prevention of pain due to injection of propofol. *Anesthesia and analgesia*. 1992; 74: 246-249. <https://goo.gl/fDzxqk>
25. Tham CS, Khoo ST. Modulating effects of lignocaine on propofol. *Anaesthesia and intensive care*. 1995; 23: 154-157. <https://goo.gl/bxwdYu>
26. Gajraj NM, Nathanson MH. Preventing pain during injection of propofol: the optimal dose of lidocaine. *J Clin Anesth*. 1996; 8: 575-577. <https://goo.gl/yJu9Uz>
27. Nathanson MH, Gajraj NM. Reducing the pain on injection of propofol. *Anesth Analg*. 1996; 82: 1307-1308. <https://goo.gl/M89ViK>
28. Parmar AK, Koay CK. Pain on injection of propofol. A comparison of cold propofol with propofol premixed with lignocaine. *Anaesthesia*. 1998; 53: 79-83. <https://goo.gl/ze3A2A>
29. Adam S, van Bommel J, Pelka M, Dirckx M, Jonsson D, Klein J. Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. *Anesth Analg*. 2004; 99: 1076-1079. <https://goo.gl/1Egduv>
30. Lee P, Russell WJ. Preventing pain on injection of propofol: a comparison between lignocaine pre-treatment and lignocaine added to propofol. *Anaesthesia and intensive care*. 2004; 32: 482-484. <https://goo.gl/jx1sfE>
31. Lilley EM, Isert PR, Carasso ML, Kennedy RA. The effect of the addition of lignocaine on propofol emulsion stability. *Anaesthesia*. 1996; 51: 815-818. <https://goo.gl/hePrpg>
32. Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. *Anesth Analg*. 2003; 97: 1646-1651. <https://goo.gl/8G6mGH>
33. Crowther J, Hrazdil J, Jolly DT, Galbraith JC, Greacen M, Grace M. Growth of microorganisms in propofol, thiopental, and a 1:1 mixture of propofol and thiopental. *Anesth Analg*. 1996; 82: 475-478. <https://goo.gl/k6jcrp>
34. Euasobhon P, Dej-Arkom S, Siriusawakul A, Muangman S, Sriraj W, Pattanittum P, et al. Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults. *Cochrane Database Syst Rev*. 2016; 2: 7874. <https://goo.gl/cD15hk>
35. Banu P, Biswas A, Naser SM, Ghosh S, Ghosh K, Mandal S. Amelioration of Pain on Injection of Propofol: A Comparison of Pretreatment with Granisetron Vs Lignocaine. *J Clin Diagn Res*. 2017; 11: 9-12. <https://goo.gl/RBUARB>
36. Agarwal A, Raza M, Dhiraaj S, Pandey R, Gupta D, Pandey CK, et al. Pain during injection of propofol: the effect of prior administration of butorphanol. *Anesth Analg*. 2004; 99: 117-119. <https://goo.gl/AbTBk7>
37. Wang W, Wu L, Zhang C, Sun L. Is propofol injection pain really important to patients. *BMC Anesthesiol*. 2017; 17: 24. <https://goo.gl/SK217U>