

A comparison of induction of anaesthesia using two different propofol preparations

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ABSTRACT

Background: Investigators have reported inter-patient variability with regard to propofol dosage for induction of anaesthesia, since early dose finding studies. With the arrival of generic formulations of propofol, questions have arisen regarding further variability in dose requirements. Various studies have confirmed that generic propofol preparations are pharmacokinetically and pharmacodynamically equivalent to Diprivan®. Nevertheless a number of practitioners are under the impression that certain generic propofol preparations require greater doses for induction of anaesthesia than does Diprivan®.

Methods: 20 female patients of ASA status I-II, between the ages of 18-55 years, scheduled for routine surgery were randomly allocated to two groups to undergo induction of anaesthesia using two different propofol formulations; Diprivan® and Propofol 1% Fresenius®. Either preparation was administered using a target-controlled infusion of propofol (STEL-TCI) targeting the plasma (central) compartment at a concentration of 6 µg.ml⁻¹, employing the pharmacokinetic parameters of Marsh et al. A processed EEG (bispectral index) was continuously recorded. Loss of consciousness (LOC) was regarded as the moment at which the patient could not keep her eyes open and was confirmed by the absence of an eyelash reflex. At this point propofol administration was discontinued and data were recorded for a further two minutes, before administering an appropriate opioid and/or nitrous oxide/volatile agent and/or muscle relaxant to maintain anaesthesia. Time to LOC after start of propofol administration, and the dose of propofol administered during induction were annotated.

Results: There were no demographic differences between the groups. There were no differences between the groups with regard to the mean dose for LOC, time to LOC and to the mean BIS values obtained at the following stages: awake, at LOC, at 1 and 2 minutes after LOC as well as the lowest recorded value.

Conclusions: Our results confirm that the two propofol formulations that we studied, are pharmacologically equivalent with regard to induction of anaesthesia. Other mechanisms can explain the variability in clinical response to bolus administration of propofol. The most important is the recirculatory or "front-end" kinetics of propofol in which cardiac output plays a major role, as well as the rate of drug administration. Emulsion degradation can also influence dose-response and in this regard it should be noted that the addition of foreign substances such as lignocaine, can result in rapid deterioration of the soya-bean emulsion.

Introduction

Investigators have reported inter-patient variability with regard to dose requirements for induction of anaesthesia (induction-doses), since early dose finding studies.¹ With the arrival of generic formulations of propofol, further questions have arisen with regard to variability in dose requirements.² In South Africa two propofol formulations are available, namely Diprivan® (AstraZeneca) and Propofol 1% Fresenius® (Fresenius-Kabi). These drugs are presented in identical soya-bean emulsion formulations, (apart from a small amount of EDTA added to Diprivan® to inhibit microbial growth). However, a number of anaesthesiologists aver that in their clinical experience, the Fresenius preparation requires greater induction-doses than those required by Diprivan®.

A number of investigators have attested that several generic propofol preparations are pharmacokinetically and pharmacodynamically equivalent to Diprivan®.^{3,5} Calvo et al reported minor differences when they examined the influence of five different emulsion formulations on propofol pharmacokinetics and pharmacodynamics; Diprivan®, Recofol®, Ivolfol®, Propofol-Abbott® and Popofol-1%-Fresenius®. The authors concluded that the pharmacokinetic properties were similar, apart from Ivolfol®, which had a smaller volume of distribution. Recofol required greater induction doses than Diprivan®. It is interesting to note that they found no difference between the mean induction-doses for Diprivan® and Popofol-1%-Fresenius®.

The purpose of this randomized, controlled study was to compare two different preparations of propofol (Propofol-1%-Fresenius® and Diprivan®) for induction of anaesthesia, including the effects

on the electroencephalogram (EEG). The hypothesis was that the two propofol formulations are equivalent, with regard to the required induction-doses, the times to loss of consciousness (LOC) and to the effects on the electroencephalogram (EEG) as measured by the bispectral index monitor (BIS).

Methods and materials

The study was conducted according to the principles of the Declaration of Helsinki. The study was approved by the Research Ethics Board of our hospital. Informed, written consent was obtained from 20 female patients of ASA status I-II, between the ages of 18-55 years, scheduled for routine surgery and who were randomly allocated to two groups to undergo induction of anaesthesia using either, Diprivan® or Propofol-1%-Fresenius®. Exclusion criteria were: body mass index >35 kg.m², uncontrolled hypertension, ischaemic heart disease, renal or hepatic dysfunction, chronic pulmonary disease, suspected substance abuse, patients who had taken herbal preparations within the previous two weeks, patients scheduled for regional anaesthesia, pregnant or breastfeeding patients, congestive cardiac failure, patients who had received opioids or sedative medication within 24 hours of the study and patients who had participated in another clinical trial within the last month. Randomisation was done according to a random number generator (<http://www.randomization.com>). Sequentially numbered sealed envelopes were prepared containing a form assigning each patient to a group. Neither the participants nor the researchers involved had any knowledge of the contents of the envelope, ensuring blinding of allocation. Only after applying the criteria of eligibility and obtaining consent from each participant were the envelopes opened. The patients were

blinded to the propofol preparation (single-blinded), but the brand name of the propofol preparation was known to the anaesthetist responsible for induction of anaesthesia and the researcher that collected the data. No premedication was administered. On arrival in the operating room, routine monitoring was instituted (noninvasive blood pressure, ECG, pulse oximetry). A large peripheral vein was used for the administration of fluid and propofol to minimize pain on propofol injection. A processed electro-encephalographic (EEG) monitor (Bispectral Index [BIS], Aspect Systems, USA) was attached and the data were recorded to computer disk using proprietary software (Dept. Anesthesiology and Intensive Care, University of Stellenbosch).

Pre-oxygenation was commenced using 100% oxygen administered by close-fitting mask at a flow rate of 6 l.min⁻¹ and the patients were instructed to keep their eyes open for as long as they could. As an additional measure to minimize pain on propofol injection, 2 ml of 2% lignocaine was administered into the vein prior to propofol injection. Induction of anaesthesia was conducted using a target-controlled infusion system (STEL-TCI, controlling a Harvard-22 syringe pump via a RS232 serial cable) (STEL-TCI: A target-controlled infusion system that is included in the STELPUMP suite of pharmacokinetic programs 2003; Authors JF Coetzee and P de Kock, Stellenbosch University.) The plasma site (central compartment) was targeted at a concentration of 6 µg.ml⁻¹, employing the pharmacokinetic parameters of Marsh et al.⁶ LOC was regarded as the moment at which the patient could not keep her eyes open and was confirmed by the absence of an eyelash reflex, and loss of verbal contact. At this point Propofol administration was discontinued and data were recorded for a further two minutes, as described below. If the patient became apnoeic, gentle, manual, intermittent positive pressure breathing was applied. On completion of data recording, the anaesthesia was further maintained by administering an appropriate opioid and/or nitrous oxide/volatile agent and/or muscle relaxant as dictated by the requirements for surgery.

Data recorded:

Demographic data included: patient body weight, height, age, sex and ASA-status. Experimental data included time to LOC after the start of propofol administration, the total dose of propofol administered, and BIS values recorded at the following times: before induction of anaesthesia, at LOC, 1 and 2 minutes after LOC.

Data analysis:

Power analyses were performed using computer software (PASS, Number Cruncher Statistical Systems, Kaysville, Utah, USA). It was presupposed that if induction doses of 1.5 mg.kg⁻¹ and 2.5 mg.kg⁻¹ (standard deviation 0.7 mg.kg⁻¹) represent clinically important differences, then group sizes of 8 each are necessary to achieve 82% power to detect such a difference. It was decided to study 10 patients in each group. An intention-to-treat analysis was used. After testing for equal

variances, inter-group comparisons were made using two-sided t-tests for independent groups (Sigmastat for Windows version 2.03, SPSS Inc, USA). Within-group comparisons were made using ANOVA for repeated measures. An alpha error of 0.05 or less was accepted as indicating statistical significance.

Results

The groups did not differ with regard to age, weight and body mass index (Table I). Results of the comparisons of the induction characteristics of the two propofol preparations are presented in Table II. There were no statistically significant differences between the following measurements: Mean induction doses of propofol (2.1 and 2.3 mg.kg⁻¹ in the Fresenius and AstraZeneca groups respectively); mean times to LOC (2.1 minutes and 2.2 minutes, with BIS-values at LOC of 46.9 and 46.7); the lowest recorded BIS values (38.2 and 33.8); mean BIS values at the following stages: awake, at LOC, at 1 and 2 minutes after LOC (Table II).

Table I: Demographics

	Fresenius Group	Astra-Zeneca Group	P	95% CI Difference
Age (years)	35.0 (5.8)	33.3 (8.4)	0.60	-5.1 to 8.5
Weight (kg)	68.6 (15.4)	71.0 (17.3)	0.75	-17.8 to 13.0
BMI (kg.m ⁻²)	26.5 (5.8)	27.8 (5.2)	0.65	-6.9 to 4.4
RPP	9996 (2852)	9663 (2353)	0.78	-2124 to 2789

Data are presented as mean (standard deviation).

BMI = body mass index;

95% CI Diff = 95% confidence interval of the difference between means;

RPP = Rate-pressure product before induction of anaesthesia.

Table II: Results

	Fresenius Group	Astra-Zeneca Group	P (t-test)	95% CI Diff	N for 80% power
Total dose (mg)	141 (38)	153 (47)	0.54	-52 to 28	200
Dose (mg/kg)	2.1 (0.6)	2.3 (0.8)	0.70	-0.8 to 0.6	197
Time to LOC (min)	2.3 (1.4)	2.2 (1.3)	0.90	-1.2 to 1.3	2865
BIS at LOC	46.9 (14.4)	46.7 (14.2)	0.97	-14.1 to 14.5	80 000
BIS awake	97.3 (1.6)	97.1 (0.7)	0.72	-0.9 to 1.4	
BIS at 1 min	43.2 (8.8)	40.9 (14.9)	0.69	-9.7 to 14.4	445
BIS at 2 min	51.7 (10.6)	48.0 (15.2)	0.56	-9.2 to 16.5	197
Lowest BIS	38.2 (8.8)	33.7 (13.9)	0.45	-8.0 to 17.0	105
Time to lowest BIS (min)	1.8 (0.9)	1.5 (0.7)	0.47	-0.6 to 1.2	114

Data are presented as mean (standard deviation).

LOC = loss of consciousness; BIS = bispectral index;

BIS at 1 and 2 min = BIS value obtained 1 and 2 minutes after LOC.

95% CI Diff = 95% confidence interval of the difference between means;

N for 80% power = Number of subjects per group in order to achieve 80% power to detect a real difference with alpha 0.05, using a two-sided, two-sample t-test.

Discussion

It is possible that this small study was insufficiently powered to detect real differences in the induction characteristics of the two propofol preparations. Power calculations were performed, using the means and standard deviations obtained from this study, in order to estimate the number of subjects that needed to be studied in order to achieve 80% power to detect real differences. These are presented in Table II. It is apparent from the required large group sizes that any real differences would probably be so small that it is unlikely that they would be of clinical importance. As there were no differences between the two groups we pooled the data and in order to extrapolate our findings to the population (women with normal body mass), we calculated the 95% confidence intervals (Table III). The wide confidence intervals probably reflect extensive inter-patient variability, however the small sample size could also have contributed thereto.

Several previously published propofol dose-finding studies used different methods to determine induction doses^{2,7,10} (Table IV). Some of these did not report 95% confidence intervals making it difficult to compare results, however from the studies presented in Table IV, it is apparent that the ED₅₀ of propofol is somewhere between 2 and 2.5 mg.kg⁻¹⁷⁻¹⁰ irrespective of the use of premedication, rate of propofol injection or method for determining the moment of LOC employed. Our results are comparable to those obtained by Calvo et al whose study was in many ways, methodologically similar to ours. Their mean induction dose was 147.2 mg (95% CI from 120.9 to 173.5) for Diprivan[®] and 163.7 mg (95% CI from 135.4 to 192.0) for Propofol Fresenius[®].² There are various explanations for the occurrence of inter-patient variability in response to rapidly administered doses of propofol that include the phenomenon of recirculatory or "front-end" kinetics, different methodological endpoints used for determining LOC and the influence of emulsion degradation.

The "front-end" kinetics of propofol:

In an editorial, Krejcie and Avram¹¹ coined the term "front-end" kinetics when commenting on studies of chronically instrumented sheep by Upton and coworkers.¹² Following rapid injection, a chain of physiological and anatomical factors, from the place of entry to the effect-site, influence the extent of drug effect and the time of onset.¹³ Firstly, drug is mixed in the venous flow before entering the pulmonary circulation through which it must undergo a first-pass before entering the systemic circulation. The lungs may delay the passage of drugs and even remove significant proportions.¹⁴⁻¹⁶ The systemic circulation then distributes drug to various organs (including the targeted organ) through which it is again subjected to a first-pass before being returned to the venous flow for recirculation. Although the liver is mainly responsible for the metabolism and elimination of propofol, some extra-hepatic metabolism (notably the lungs and kidneys) does occur.^{17,18} Various studies have indicated that cardiac output has a particularly important influence on blood drug concentrations according to the same principle by which dilution of injected

tracer is used to measure cardiac output.^{12,19} As cardiac output increases, peak arterial concentrations decrease in response to a bolus dose and the area under the arterial concentration-time curve decreases, leading to decreased effects on the targeted organ. Distribution of arterial blood flow to the brain also plays an important role in determining the extent of drug effect: The greater the cerebral blood flow, the higher the peak brain concentrations and the greater the effects.²⁰ It is interesting to note that propofol reduces cerebral blood flow^{21,22} and it is possible that this may affect its own uptake into the brain.

It is apparent that the traditional two (or three)-compartment mammillary models that are used to express the disposition of intravenously administered drugs, are inadequate to describe the early pharmacokinetics and pharmacodynamics of short, rapid infusions ("bolus" doses). These models assume that drugs distribute immediately and homogeneously within a "well-stirred" central compartment, before undergoing distribution to peripheral compartments. After injection, the decreasing arterial plasma concentrations are described by an expression that consists of the sum of two or more exponential terms. This "polyexponential" model miss-specifies the early time course of drug concentration, because it assumes the central compartment to be homogeneous rather than a complicated system of organs in series and parallel.²³ Krejcie et al²⁴ have demonstrated the occurrence of multiple blood concentration-peaks after bolus injection, particularly during the first minute, probably due to rapid recirculation. Because traditional compartmental models are represented by monotonic functions, these recirculatory oscillations cannot be described by conventional compartmental models.

Hybrid models that incorporate circulatory physiology (including lung kinetics and recirculation phenomena) into compartmental models satisfactorily predict the early time course of propofol concentrations in the circulation and the brain.²⁵ The simplest model consists of two compartments, the lungs and the rest of the body.²⁶ Drug administration is into the "lung" compartment (which receives the total cardiac output) and clearance is from the "body" compartment. These models have been developed further and expanded to include cerebral blood flow and dynamics. They are able to simulate the complex effects of circulatory changes on the pharmacokinetics and pharmacodynamics of propofol in sheep,^{12,20,27-29} as well as in humans.²⁵

The rate at which propofol is administered can influence the blood concentrations. Simulations using the hybrid model of Upton and Ludbrook³⁰⁻³² demonstrate that after rapid intravenous injection, brain concentrations increase rapidly and continuously after termination of the infusion, because the greater mass of propofol is still in transit through the lungs and has yet to reach the brain. As a result, rapid injection rates produce high peak concentrations in arterial blood and a subsequent overshoot of brain concentrations. Little benefit is achieved in terms of decreased induction times and furthermore high plasma

Table III: 95% Confidence intervals of the pooled data indicating degree of variability.

	Mean	SD	Range		95% Confidence Interval of the mean
			Min	Max	
Total Dose (mg)	147	42	97	263	128 to 167
Dose in mg/kg bodyweight	2.2	0.7	1.4	3.8	1.9 to 2.5
Time to LOC (min)	2.2	1.3	0.6	5.0	1.6 to 2.8
BIS awake	97	1.2	93	98	96.6 to 97.8
BIS at LOC	46.8	13.9	28	82	39.9 to 53.7
BIS at 1 min	42.0	12.1	13	66	36.1 to 47.9
BIS at 2 min	49.7	13.0	24.0	71	43.5 to 56.0
Lowest BIS	35.9	11.5	11.1	57.3	29.8 to 42.0
Time to lowest BIS (min)	1.6	0.8	0.8	3.8	1.2 to 2.1

Table IV: Dose finding studies for propofol dissolved in a lipid emulsion.

	Dosing method	Propofol preparation	Dose (mg)	95%CI Dose (mg)	Dose (mg/kg)	95%CI Dose (mg/kg)	Method LOC	Time to LOC (s)	95%CI (s)	Premed	n
Cummings et al.⁷	Predetermined dose over 20s	Diprivan ED ₉₅	168.8	N/A	2.5	N/A	Stop count	26.7	25.6 to 27.8	No	84
							Drop syringe	34.3	32.1 to 36.5		
							LOR	51.8	47.0 to 56.6		
Grounds et al.⁸	Injection over 20s after releasing tourniquet	Diprivan ED ₅₀	92.1	N/A	1.3	1.2 to 1.6	Drop syringe	<90 s	N/A	No	56
		ED ₉₅	175.9	N/A	2.6	N/A		<90 s	56		
Naguib et al.⁹	Injection over 15s into rapidly flowing infusion	Diprivan ED ₉₅ @ 30s	167.7	N/A	2.7	N/A	Stop count & LOR	30s	N/A	No	36
		ED ₉₅ @ 60s	138.8	N/A	2.2						
		ED ₉₅ @ 90s	136.9	N/A	2.2						
Calvo et al.²	Fast infusion At 600ml.h ⁻¹	ED ₉₅ Diprivan	147.2	130 to 164.4	2.0	1.8 to 2.3	BIS 60/ LOR	N/A	N/A	Yes	20
		Fresenius	163.7	144 to 183.4	2.3	2.0 to 2.5					18
Terblanche & Coetzee	Target-controlled infusion	ED ₉₅ Diprivan	153	119.4 to 186.6	2.3	1.7 to 2.9	LOR	132	76.2 to 187.8	No	10
		Fresenius	141	113.8 to 168.2	2.1	1.7 to 2.5		138	77.9 to 198.1		10

Legend to Table IV:

95% CI Diff = 95% confidence interval
 ED₅₀ = effective dose of propofol that will reliably induce anaesthesia in 50% of patients
 ED₉₅ = effective dose of propofol that will reliably induce anaesthesia in 95% of patients
 LOC = loss of consciousness
 Premed = premedication
 BIS = Bispectral index
 Loss count = loss of verbal contact
 LOR = loss of eyelid reflex
 N/A = not available

concentrations of propofol can lead to hypotension mediated by both arterial and venous dilatation. Slower propofol injection rates, induce anaesthesia almost equally rapidly, using smaller doses and with better titration to LOC. The optimal duration of an injection of a bolus of propofol appears to be one to two minutes, possible benefits being reduced dosage, reduced overshoot in depth of anaesthesia after the desired end-point has been reached and reduced peak arterial concentrations, which may have haemodynamic advantages.^{33,34} Longer injection times predictably lead to prolonged induction times. Our TCI system administered a mean dose of 147 mg during 2.3 minutes, producing LOC after 2.2 minutes. This is not unduly greater than the times to LOC that occurred when propofol was administered during 15 to 20 seconds (Table IV). Furthermore, there was considerable variation in the times to LOC as evidenced by the wide standard deviation and 95% confidence interval (Table III).

The influence of the endpoint for LOC:

Dose-finding studies for propofol have utilised various endpoints to determine the moment at which LOC occurs.^{7,35,36} Abolition of response to verbal command signifies a lighter level of anaesthesia than releasing a grasped object. Loss of eyelash reflex represents an even deeper level of anaesthesia.¹⁰ The latter method has been regarded by some as an unreliable method for determining the moment of LOC.⁷ The most reliable sign, releasing a grasped object, is too cumbersome for routine clinical use. Electroencephalographic (EEG) monitors provide a more objective means of determining the hypnotic effects of drugs,³⁷ however they do not reflect the moment of LOC reliably, because of the time lag that is interposed between LOC and EEG changes. In

spite of its perceived shortcomings, loss of eyelash reflex remains the most commonly used method to determine LOC.

The effects of emulsion formulation of propofol:

Propofol is highly lipophilic and has a small molecule size, therefore good miscibility with water can be achieved using lipid emulsions. An emulsion is defined as a mixture of two immiscible substances. The addition of an emulsifier stabilises an emulsion by forming a charged, protective layer around the emulsified droplets that prevents adhesion and coalescence. The soya bean oil emulsion formulation for propofol is identical to the parenteral fat formulation, Intralipid®. The oil droplets contain the dissolved propofol, while phospholipids from purified egg lecithins serve as the emulsifier.³⁸ Glycerol renders the mixture isotonic with blood and sodium hydroxide induces optimal emulsion stability by preserving the pH at 7-8.5. At this pH the emulsion is charge-stabilised with a zeta potential of -40 to -50 mV.³⁹

Upon intravenous administration the drug diffuses across the droplet interface, entering the bloodstream. The rate of propofol release depends on three main factors, the drug concentration-gradient, the partition coefficient and the interfacial area of the droplets. The latter is in turn dependent on the size of the oil droplets.³⁸ These should be small enough to allow rapid release, to pass through capillaries and to be physically stable. Propofol emulsion droplets are typically the size of chylomicrons (0,15-0,3µm).⁴⁰ Ward et al⁴¹ performed a double-blind, crossover study that compared IDD-Propofol with Diprivan. IDD-Propofol is an alternative formulation in which propofol is dissolved in a 2% emulsion of medium-chain triglycerides. Although induction times were 14 % longer with IDD- Propofol than with Diprivan, the differences were not clinically important.

An emulsion's stability depends on the formation of a mechanical barrier by the emulsifier between the oil droplets and the aqueous phase, as well as on the presence of negative electrostatic repulsive forces between oil droplets (zeta potential). Emulsion degradation occurs over time as follows.³⁸ Suspended droplets collide either naturally (Brownian motion) or due to external agitation. Upon collision, attractive forces (van der Waal

interactions) overcome the repulsive forces, causing droplets to adhere in a state called flocculation. In this state the thin aqueous film between two adhered droplets can rupture causing the oil of the droplets to combine, creating a larger but still emulsified droplet, a process termed coalescence. Continuing coalescence yields droplets of increasing larger size, which can rise towards the emulsion surface (creaming). Both flocculation and creaming are reversible by agitation. As soon as droplets become sufficiently large enough so that free oil is formed on the emulsion surface, they cannot be reduced in size except by re-homogenisation.³⁹ The formation of larger droplets decreases the total surface area resulting in slower rates of propofol release, so that emulsion degradation can influence the induction dose. Creaming also results in the uneven distribution of drug concentration in the ampoule, which can influence the amount of propofol that is drawn into a syringe and injected.

There are several factors that can promote emulsion degradation:

- Decreased pH: Fatty acids released by the phospholipids, decrease pH and destabilise the emulsion by decreasing the zeta potential. Han has shown that a propofol emulsion containing sodium metabisulphite (to inhibit microbe growth) has a pH 4.5-6.4 and is less stable than Diprivan.³⁹
- The presence of cations: Cations (Na⁺, K⁺, Ca⁺⁺ etc.) neutralise the negatively charged repulsive forces on the droplet surfaces.³⁸
- Addition of lignocaine: Lilley et al⁴³ showed that the addition of lignocaine decreased the zeta potential of the droplets. At concentrations greater than 10 mg.ml⁻¹ the mean droplet size increases significantly.^{44,45}
- Other factors that promote emulsion degradation include increases in temperature, excessive agitation and freeze thawing.³⁹

Emulsion degradation could have contributed to some of the inter-patient variability observed in our study, however sodium edetate (not sodium metabisulphite) is used as the antimicrobial agent in Diprivan[®] and the Fresenius preparation is without preservative. Furthermore, considering that no lignocaine was added to the propofol preparations, it is unlikely that emulsion degradation played a major role in our study.

Conclusions

Our results indicate that the two studied propofol formulations are pharmacologically equivalent and that following intravenous injection, there are no differences between the doses required, the times to LOC and the effects on the EEG as measured by the bispectral index monitor (BIS). Several mechanisms can explain the variability encountered in clinical response following "bolus" administration. The most important are variations of the recirculatory or "front-end" kinetics of propofol, in which cardiac output plays a major role. This can, for example, explain the greater induction doses required for a young, anxious, tachycardic patient, compared to an elderly patient with a low resting cardiac output. Other mechanisms may include the rate of administration and emulsion degradation. It is important that propofol ampoules that have exceeded their expiry date should be discarded, particularly if oil droplets are visible on the fluid surface, as this indicates an advanced stage of emulsion deterioration. Ampoules of propofol should be agitated before drawing into a syringe as invisible creaming may have occurred during storage. If lignocaine is mixed with propofol, not more than 10mg should be added to a 20ml ampoule and the solution should be used immediately.

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Conflict of interest: None

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