Romanian Journal of Anaesthesia and Intensive Care 2016 Vol 23 No 1, 7-11
ORIGINAL ARTICLE
DOI: http://dx.doi.org/10.21454/rjaic.7518.231.emf

Propofol emulsion-free drug concentration is similar between batches and stable over time

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Abstract

Despite their widespread use for anesthesia and sedation, propofol emulsions have several unresolved issues, including pain on injection, stability concerns, and propensity to support bacterial growth. Pain accompanying a propofol injection has been attributed to the amount of free as opposed to emulsified propofol in the blood, which can differ with the formulation. Emulsions are inherently unstable and subject to several types of destabilization, but the actual mechanism may vary between formulations or batches. Free drug concentration and emulsion stability have not been widely studied between batches of propofol emulsions. Verifying whether batch-to-batch variability is a contributing factor to pain on injection or emulsion destabilization will help us better assess the causes and guide the design of future propofol formulations.

Methods. Several samples of generic 1% propofol emulsion from various batches were compared. Free drug concentration was measured using an equilibrium dialysis method. Emulsion stability was evaluated by visible observation and by measuring droplet size distribution and polydispersity during shelf storage for up to 21 months.

Results. Small differences in free drug concentration were observed between samples (10.6-16.7 μg/mL), but these differences were not statistically significant ($p > 0.05$). Emulsion droplet size (235.4-221.1 nm) and polydispersity (0.115-0.095) did not differ statistically over 21 months of storage. All batches were resistant to creaming and other destabilization mechanisms.

Conclusions. Batch-to-batch variability does not significantly alter the free drug concentration or stability of propofol formulations. If pain on injection of propofol is in fact related to the free propofol drug concentration, then it is unlikely that batch-to-batch variability causes any changes in pain on propofol injection.

Keywords: propofol, emulsions, pain on injection, batches, emulsion destabilization

Received: 23 November 2015 / Accepted: 23 February 2016 **Rom J Anaesth Int Care 2016; 23: 7-11**

Introduction

Propofol is widely used as a general anesthetic and sedative, with rapid onset and recovery from anesthesia. However, an injection of propofol is often accompanied with moderate to severe pain localized near the injection site [1-3]. Reports of pain on injection are varied and are often attributed to many different factors, including the size of the vein used for injection, pretreatment with local anesthetics or other drugs, injection technique, temperature of the dose, and formulation, among others [1, 2]. Differences between brand and generic versions [4] and the excipients used (pure long-chain triglycerides or mixtures of medium- and long-chain triglycerides) [5] are among the formulation considerations that potentially influence the pain that patients often experience with a propofol injection.

Propofol is formulated as an oil-in-water emulsion because of its low water solubility. Like other phenolic compounds, propofol is a membrane irritant [6]. The

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pain on injection has been linked to the free propofol drug concentration, or the amount of drug freely dissolved in blood [7, 8]. After an injection of propofol, the free drug concentration local to the injection site is affected by two factors: the emulsified propofol begins to dissolve after injection into the blood [9], but the much more likely factor is the amount of propofol freely dissolved in the emulsion continuous phase immediately mixing with the bloodstream at the intravenous injection site. Previous studies have shown that the aqueous concentration of propofol is not negligible and contributes to pain on injection [8, 10]. Pain response from propofol in the emulsion aqueous phase is likely greater if the emulsion is injected into veins with narrow diameters and lower blood flow rates, because the emulsion does not mix and dilute with the blood as well.

There are also concerns about the stability of propofol emulsions [11]. Often, to limit or prevent the pain caused on injection, the injection site vein is pretreated with a local anesthetic (lidocaine) or, alternatively, local anesthetic may be added to the propofol formulation prior to injection [2]. However, mixing lidocaine with propofol emulsions has been linked to emulsion destabilization [12]. There is also a concern that the antimicrobial additives that are part of the formulation may themselves lead to destabilization of the propofol emulsion [13]. The mean droplet diameter of propofol emulsions is reported to be between 150 and 300 nm; larger emulsion droplets are more susceptible to destabilization mechanisms of creaming, heterogeneous coalescence, and phase separation [14]. Emulsion droplets above 5 μm in diameter create a risk of embolism or capillary occlusion upon injection [11, 15].

In this study, we investigated whether batch-to-batch variability or shelf time leads to differences in free drug concentration or droplet size. We ultimately intended to determine whether the production batch age is itself a, previously unconsidered, variable that affects the free propofol concentration and therefore has an effect on emulsion stability and thereby potentially also pain on injection.

Methods

Four convenience samples of generic 1% (w/v) propofol emulsions [Fresenius-Kabi AG (Sweden), distributed by Abraxis Pharmaceutical Products (Schaumburg, IL, USA)] were studied. These emulsions were formulated with long-chain triglycerides and also contained ethylenediaminetetraacetic acid (EDTA) as the preservative. Each emulsion sample was from a different production batch and had a different expiration date, but all samples were from the same manufacturer (Table 1).

Free drug concentration

We measured the free drug concentration of each propofol formulation using a dialysis method adapted from a previous study [10]. We added 3 mL of emulsion to a well-rinsed section of dialysis tubing (12-14 kDa molecular weight cut-off). The tubing was sealed at both ends and tested for leakage prior to immersion in 25 mL of dialysis media. We used a solution of 2.25% glycerol in deionized water (w/w) as an isotonic dialysate for propofol emulsions. Samples of dialysate were collected several times until equilibrium was achieved at approximately 48 h. Propofol concentration was determined by high-performance liquid chromatography (Waters Acquity, Milford, MA, USA) using a C18 column with a 50:50 volume ratio of acetonitrile:water as the mobile phase at 1 mL/min flow rate. Propofol peaks eluted at approximately 4.5 min were analyzed with an ultraviolet-visible spectrophotometry detector at 270 nm. Experiments were performed in triplicate.

Confidence intervals (95%) were calculated for each sample and compared to determine whether differences in free concentrations between samples were statistically significant.

Emulsion stability

We qualitatively and quantitatively assessed the stability of each generic formulation. We measured droplet size distribution of each emulsion at set intervals for up to 21 months of shelf storage. Droplet size distributions and polydispersity were collected using dynamic light scattering (Zetasizer Nano; Malvern, Worcestershire, United Kingdom). We also visually inspected the samples for any indication of creaming and/or color change. Photos of the emulsions were taken at various times during shelf storage. Changes in emulsion droplet size distribution or any creaming are an indication of an unstable emulsion.

Results

Table 1 lists the four generic propofol formulations evaluated for free drug concentration and long-term stability. Although the samples were noted as "DIPR", these samples are not Diprivan®, rather the generic formulation of 1% propofol manufactured by Fresenius-Kabi AG. All samples were manufactured in Sweden from several different production batches indicated by the lot number on the vial. The expiration dates ranged 6 months, from November 2014 to April 2015, indicating these samples were likely manufactured within 6 months of each other. Table 1 also lists the mean values of free drug concentration obtained from the dialysis analyses.

Figure 1 shows the mean values and 95% confidence intervals of free drug concentration from each propofol

Table 1. Propofol emulsion samples

Sample	Batch lot no.	Expiration date	Analysis date	Mean free propofol concentration (mg/mL)
1	10FM6534	Nov 2014	Sept 2013	0.0137
2	10GB8469	Jan 2015	Sept 2013	0.0149
3	10GC9870	Feb 2015	Sept 2013	0.0106
4	10GE3405	Apr 2015	Sept 2013	0.0167

sample. The confidence intervals for all samples overlap, indicating that the differences in free drug concentration between samples are not statistically significant.

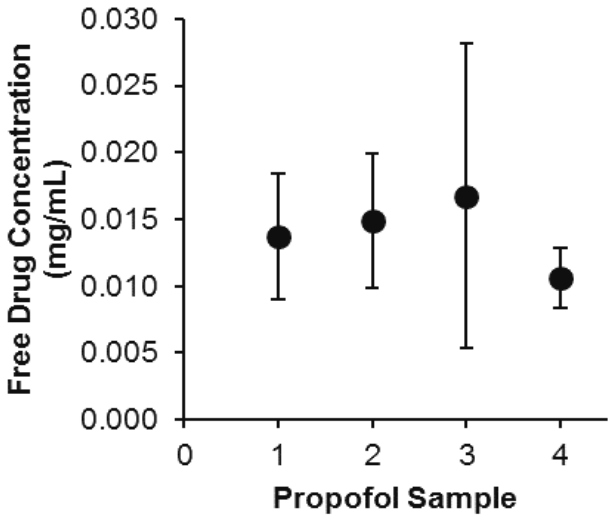

Fig. 1. Mean values of free drug concentration from several batches of propofol emulsion. Error bars indicate 95% confidence intervals (n = 3)

Figure 2 shows two images of the same propofol emulsions at different shelf life times. No visible creaming was observed in over 21 months of shelf storage at room temperature, indicating that these emulsions are stable as would be expected from their future expiration date. No major differences in emulsion stability between the propofol batches can be observed visually. Some discoloration or yellowing of the emulsion was observed at longer times; this discoloration is attributed to propofol dimerization, in particular, the quinine form of the dimer, which has a yellow color [16]. Dimerization is an oxidative process that occurs naturally in propofol emulsions when exposed to oxygen. Commercial vials of propofol emulsion are sealed under nitrogen until use and stored from 4 to 25°C [17], thus dimerization is unlikely to occur in commercial formulations until the expiration date.

Figure 3 shows the mean droplet size and polydispersity index of each propofol emulsion at different shelf life storage times. There was very little deviation between samples, and also no major change in droplet size over time on the shelf. After 21 months, the droplet size was very similar to the initial size, indicating that although the emulsions are thermodynamically unstable, they are very kinetically stable. Polydispersity indices of all samples are below 0.15 and do not increase even after 21 months of shelf storage, indicating that not only do the average droplet sizes remain constant, the larger droplets do not coalesce and smaller droplets are not absorbed through Ostwald ripening [14].

Discussion

The results of this study demonstrate that there is very little difference between batches or shelf time of the generic propofol emulsions studied. Free drug concentrations were observed to differ slightly between samples, but the differences were not statistically

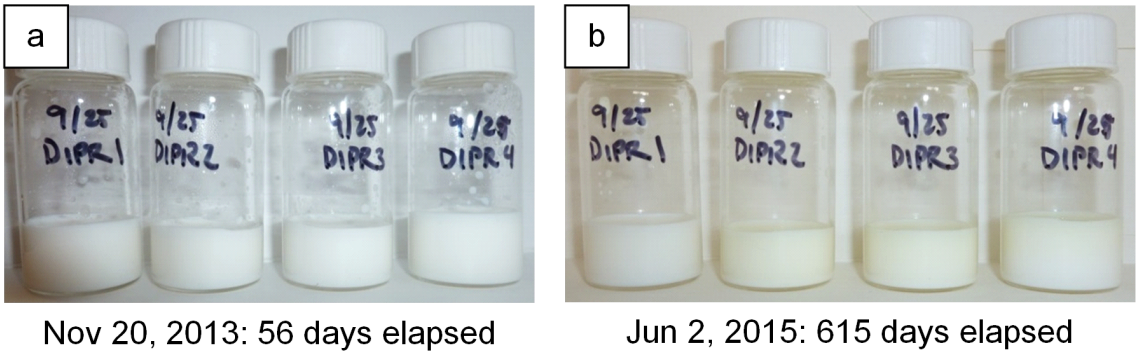

Fig. 2. Photographs of the same four propofol emulsion samples at: a) 56 days of shelf storage and b) 615 days of shelf storage

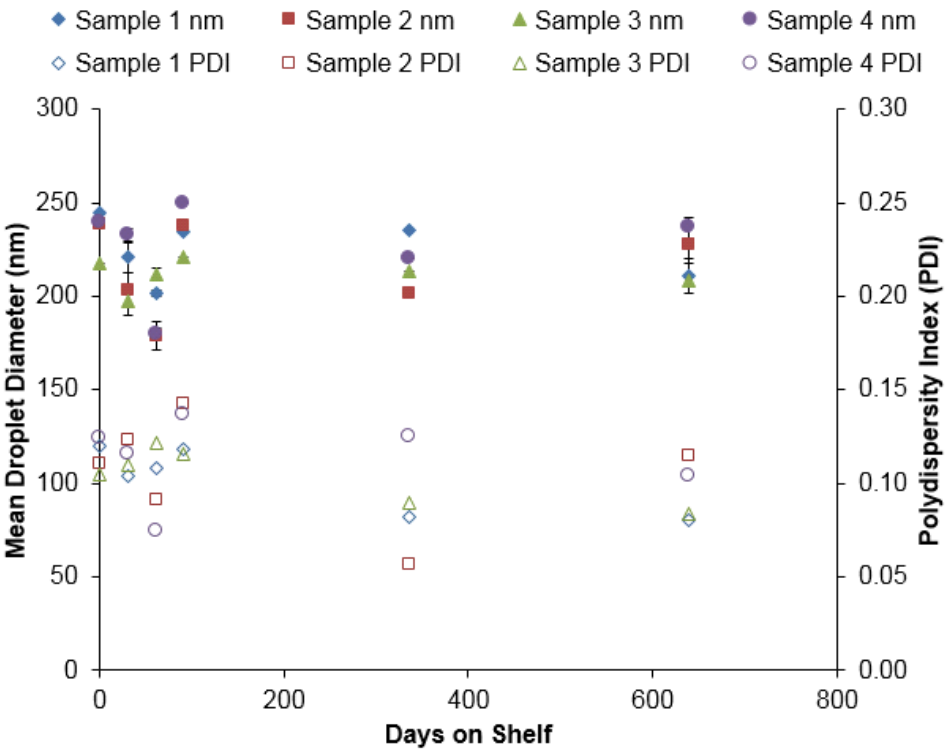

Fig. 3. Mean droplet diameter (filled shapes) and polydispersity index (open shapes) of propofol batches at different durations of shelf storage. Error bars indicate standard deviations (n = 3)

significant. It is therefore unlikely that batch-to-batch variability in the free propofol concentration is a factor influencing pain on propofol injection. Pain on injection is likely more influenced by the vein chosen for injection [2], as well as by different emulsion formulations such as those with excipient oils containing medium-chain triglycerides [5, 18, 19] or other novel excipients [10], as these may significantly affect the free drug concentration local to the injection site. Droplet size distributions and degrees of polydispersity do not substantially vary between batches, indicating that emulsion stability is consistent between batches of the same formulation. Mixing of propofol with local anesthetics such as lidocaine [12] or improper storage conditions during shelf storage or improper storage [13] can both cause destabilization of the propofol emulsion. Either of these two factors is more likely a cause of emulsion destabilization rather than batch variability.

Conflict of interest

Nothing to declare

Funding

Support for this work was solely through institutional and departmental sources

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Concentrația formei libere de propofol în emulsie este similară între loturi şi stabilă în timp

Rezumat

În ciuda largii lor utilizări pentru sedare şi anestezie, emulsiile de propofol au câteva inconveniente nerezolvate, care includ durerea la injectare, probleme legate de stabilitate şi de susceptibilitatea de a favoriza dezvoltarea bacteriană.

Durerea pe care o provoacă injectarea de propofol a fost atribuită concentrației libere de propofol din sânge, care poate fi diferită de la un preparat la altul. Emulsiile sunt prin definiție forme chimice instabile şi sunt predispuse la diverse forme de destabilizare, însă mecanismul acestei destabilizări poate fi variabil, în funcție de forma farmaceutică şi/sau lotul de fabricație. Concentrația liberă de propofol şi stabilitatea emulsiei în loturi diferite de emulsii de propofol nu a fost larg studiată până la această dată. Verificarea faptului că variabilitatea de la un lot la altul a emulsiei de propofol poate reprezenta un factor care contribuie la determinarea durerii la injectare sau a instabilității emulsiei ne va ajuta să apreciem mai corect cauzele şi va ghida spre eventuale noi formule de preparare a propofolului.

Metodă. Au fost comparate câteva mostre de emulsie de propofol 1% din diferite loturi de fabricație. Concentrația liberă de propofol a fost determinată utilizând o metodă de echilibrare de tip dializă. Stabilitatea emulsiei a fost evaluată prin observație macroscopică, măsurând distribuția picăturilor şi polidispersia de-a lungul depozitării, pe o perioadă de 21 de luni.

Rezultate. Au fost observate mici diferențe de concentrație a propofolului între mostrele analizate (10,6-16,7 μg/ml), dar aceste diferențe nu au fost semnificative statistic ($p > 0,05$). Dimensiunile picăturilor emulsiei şi polidispersia (0,115-0,095) nu au fost diferite din punct de vedere statistic de-a lungul celor 21 de luni de depozitare. Toate loturile s-au dovedit rezistente la decantare sau la alte mecanisme de destabilizare.

Concluzii. De la un lot la altul, variabilitatea produsului nu a afectat semnificativ concentrația liberă de propofol sau stabilitatea preparatelor. Dacă durerea de injectare la propofol este legată de fapt de concentrația liberă de propofol, atunci este puțin probabil ca variabilitatea loturilor să determine modificări în durerea determinată de injectarea de propofol.

Cuvinte cheie: propofol, emulsie, durere la injectare, loturi, destabilizarea emulsiei