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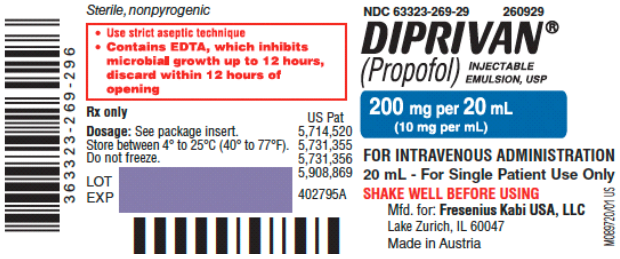
EDITORIAL

# Propofol: to shake or not to shake

"Shake well before using." It is easy to overlook these four words on the label of each propofol bottle. Although this instruction appears as a "Red Label Warning" (Fig. 1), we believe this is not well known or followed in clinical practice. Why is it necessary to "shake well before using"?




Propofol (2,6-diisopropylphenol), a sedative and hypnotic, is one of the most commonly used drugs in anesthesia practice. Due to its poor water solubility (octanol: water partition coefficient of 6761:1), it must be formulated in an oil-in-water (O/W) emulsion. That is, the propofol is dissolved in the oil phase, which in turn is formed into tiny droplets within the aqueous phase. Depending on the properties of the oil phase, the partitioning efficiency and emulsion stability can be changed [1]. Using short chain triglycerides, such as ethyl butyrate for the oil phase, can result in better drug partitioning but decreased stability, while using long chain triglycerides, such as soy bean oil, yields a decrease in drug partitioning but increased stability.

It is well known that one of the primary problems encountered with propofol is pain during injection, which is reported by about 60% of patients [2]. Several contributing factors to the pain have included the particular injection site, vein size, speed of injection, injectate temperature, and aqueous propofol concentration [3]. However, there is substantial evidence that favors the aqueous propofol concentration as the main contributing factor to pain with the injection of propofol [4, 5].

If propofol partitioning and emulsion stability can be altered by the formulation, one must wonder if the aqueous propofol concentration might vary from batch to batch or become unstable over time. Is this the reason for the "Red Label Warning"? The manufacturer must question the stability of propofol, because one propofol package insert states:

> *Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.*

Although not well known in the anesthesia community, there are data that some propofol emulsions are actually prone to increased droplet size with excessive shaking [6].

In their accompanying article in the *Romanian Journal of Anaesthesia and Intensive Care*, Damitz and colleagues [7] studied the aqueous propofol concentrations among different batches of propofol, as well as emulsion stability over 21 months of storage. Four samples of generic 1% propofol emulsions were obtained with different production batch numbers and expiration dates. The aqueous drug concentration was measured using a previously adapted dialysis method and high-performance liquid chromatography, and droplet size and polydispersity index were measured using dynamic light scattering. The initial aqueous concentration of propofol was not significantly different between the four samples tested. The initial mean

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droplet diameter was between 180 and 250 nm, which remained remarkably consistent over the 21 months of shelf storage. The polydispersity index, which is a measure of droplet size heterogeneity, initially was measured between 0.05 and 0.15 and also remained constant over the 21 months of shelf storage.

These data suggest that the initial batch-to-batch variability of the aqueous propofol concentration is minimal and unlikely to influence pain on injection. Additionally, they have shown that there is little change in oil droplet size and polydispersity over time, suggesting that propofol emulsions are very stable. However, the stability of aqueous propofol concentration was not measured over time. Therefore, it remains a possibility that aqueous propofol concentrations could increase with long storage periods causing increased pain on injection.

Newer formulations of propofol have been developed to reduce injection pain by taking advantage of the increased drug partitioning of shorter chain triglycerides while maintaining the stability of longer chain triglycerides. Yamakage and colleagues reported that by using a mix of medium and long chain triglycerides, the aqueous propofol concentration was decreased by up to 40% compared to using only long chain triglycerides [8]. It has also be shown that using a medium/long chain triglyceride propofol emulsion reduced the injection pain incidence to 47% compared to 60% when using a long chain triglyceride propofol emulsion [9].

In addition to altering the propofol emulsions, other interventions to prevent pain on injection have been suggested. The most effective methods of pain reduction included use of the antecubital vein, lidocaine pretreatment with venous occlusion, mixing propofol with lidocaine, lidocaine pretreatment without venous occlusion, opioid pretreatment, ketamine pretreatment, and NSAID pretreatment [2].

We applaud the work by Damitz and colleagues [7], who have added to our body of knowledge regarding the administration of propofol. It appears that "shake well before using" may not be necessary.

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**Conflict of interest**

Nothing to declare

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