Exploring the frontiers of propofol formulation strategy: is there life beyond the milky way?

From clinical, scientific, and commercial perspectives, propofol is a fabulous success. In addition to its popularity as an i.v. induction agent, propofol is widely used internationally for the maintenance of general anaesthesia. Coupled with target-controlled infusion technology, the introduction of propofol launched the total i.v. anaesthesia (TIVA) revolution that must be regarded as one of the most significant innovations in anaesthesia practice of the last half century. And propofol’s popularity is not limited to the operating theatre. Propofol is also commonly used for the provision of sedation in procedural suites and intensive care units around the world.

Despite its success, however, propofol’s current formulation has a number of undesirable properties that are in part a function of the lipid emulsion formulation approach. This lipid-based formulation frequently produces pain on injection and has also been associated with serious allergic reactions. In addition, because the lipid formulation supports rapid microbial growth, inadvertent contamination of the formulation can be a cause of postoperative sepsis, a problem that persists despite antimicrobial additives. Finally, hyperlipidaemia may be a risk factor in the development of the propofol infusion syndrome, an often lethal metabolic disorder typically associated with prolonged propofol administration in the intensive care unit. For this reason, there is substantial interest in the development of new formulations of propofol that are devoid of some or all of the undesirable features of the current lipid-based formulation.

Creating a formulation that enables the i.v. delivery of propofol is a significant challenge for pharmaceutical chemists. Poured into a beaker of water, raw propofol looks and behaves like vegetable oil. It can be seen as a distinct, translucent, yellow layer floating on top of the water. Indeed, propofol does not mix easily with water; its miscibility is extremely limited (i.e. about 150 μg litre⁻¹). To address this problem, propofol was ultimately developed as a lipid-based macroemulsion containing soybean oil, egg yolk lecithin, and glycerol (Diprivan, AstraZeneca, London, UK). In this formulation, resembling Intralipid (Fresenius Kabi, Homburg, Germany), the oil droplets containing most of the propofol are large enough to reflect and refract white light significantly. Thus, the lipid-based macroemulsion looks a lot like milk (i.e. this formulation can be thought of as the ‘milky way’).

Given the problems associated with the current lipid-based formulation (and propofol’s commercial success), it is not surprising to learn that a number of propofol formulations utilizing a wide variety of pharmaceutical technologies have been investigated. These include an array of lipid-based emulsions (typically attempting to reduce the total lipid content), non-lipid excipients (e.g. surfactants–co-surfactants, nano-particle carriers, cyclodextrins) and a prodrug.

A substantial challenge associated with the reformulation of propofol is that reformulation may alter propofol’s pharmacokinetic and pharmacodynamic characteristics. On the basis of information from animal studies, it appears that at least some of propofol’s rapid-onset, rapid-offset clinical pharmacologic profile is dependent on the formulation. Thus, for propofol, a simple and important maxim for pharmaceutical chemists is that changing propofol’s formulation may change its clinical pharmacology.

This issue of the British Journal of Anaesthesia includes a straightforward illustration of this maxim. Jung and colleagues report their experience with a new, microemulsion formulation of propofol called Aquafol (Daewon Pharmaceutical, Seoul, Korea). Utilizing surfactants and co-surfactants to emulsify the propofol in water, Aquafol is a newly developed microemulsion propofol formulation that is a colourless liquid containing propofol 1%. The authors performed a carefully designed clinical pharmacology experiment in patients designed to compare
the pharmacokinetics and pharmacodynamics of Aquafol™ with propofol in lipid (Diprivan®). Although the kinetics and dynamics of the two formulations were ‘substantially similar’, a major difference was that patients who received propofol in the non-lipid, microemulsion form experienced a lot more pain on injection. Although the pain on injection associated with propofol is perhaps not a major adverse event, it is nonetheless regarded as an important unsolved problem in clinical anaesthesia. Aquafol™ may eventually be shown to mitigate some of the problems associated with the lipid contained in Diprivan® (and similar formulations), but it will apparently come at the cost of increased pain on injection. In any case, the key point is that formulation matters!

Regardless of the pharmaceutical technology used to formulate and deliver propofol, it is clear that the impact of a novel formulation on propofol’s clinical pharmacology must be investigated carefully. The formulation strategy is not just a ‘vehicle’ to deliver the drug; as for propofol, the formulation strategy is an integral part of the drug.

The literature relating to alternative propofol formulations is replete with cases in point. For example, formulations with a lower lipid content typically exhibit more pain on injection compared with Diprivan® and similar products. Propofol as a ‘phosphate prodrg’ (i.e. fospropofol), perhaps as expected, has a slower onset than propofol in a lipid formulation. Propofol formulated in polymeric micelles, an approach that can be considered a ‘nano’ delivery system because of the very small size of the copolymer particles used to form the micelles, results in a transparent solution that allows the natural antimicrobial effect of propofol’s phenol to be manifest. The novel micellar and microemulsion propofol formulation strategies, because they do not utilize lipids, may presumably address some of the concerns related to the exogenous lipid administration associated with Diprivan® and similar formulations. This is obviously of increased importance in therapeutic areas where propofol is administered for prolonged periods such as in intensive care units. These alternative propofol formulation approaches are at various stages of development, ranging from preclinical to post-marketing phases.

For a new propofol formulation to be truly successful, there are at least four challenges to be overcome: first, it must be technically feasible to move the formulation from the laboratory to clinical use on an industrial scale. Secondly, the formulation must be clinically useful, offering some new advantage. Thirdly, the novel formulation must achieve regulatory clearance, meeting the criteria of international regulatory agencies. Finally, the new formulation must be well received by the market; that is, clinicians, funders, and patients must see it as offering good value for the cost. Given the well-entrenched role of the lipid-based formulation in modern anaesthesia practice, especially at a generic price, market receptivity is likely to be the greatest challenge for any new propofol formulation.

As we look to the future through an admittedly speculative lens, what do we see for these novel propofol formulations? As anaesthesia investigators explore the outer limits of propofol formulation pharmaceutical strategies, will they find life beyond the ‘milky way’? Is it conceivable that one or more of these alternative propofol formulation strategies could actually gain widespread acceptance or even replace the lipid-based formulation? Only time will tell, of course, but certainly we can see some intriguing possibilities.

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**References**


This issue of the *British Journal of Anaesthesia* includes an article describing tracheal intubation of children under sevoflurane/alfentanil anaesthesia without any neuromuscular blocking agent.\(^1\) The authors demonstrated that the technique is feasible and used Dixon’s up-and-down method to estimate the ED\(_{50}\) of alfentanil for this purpose in the presence and absence of nitrous oxide. These observations, together with many others, confirm that intubation without neuromuscular blocking agents is feasible; however, the question remains as to whether it is useful. This editorial critically addresses that question and challenges the motivation of clinicians using the technique.

How can we intubate the trachea without neuromuscular blocking agents? In addition to awake intubation, itself the subject of many editorials and different techniques, we have distinct choices when attempting neuromuscular blocking agent-free tracheal intubation during general anaesthesia.

Tracheal intubation during deep inhalation anaesthesia has been practised since anaesthesia began. Currently, it is reserved for children and occasionally as one possible strategy for addressing known or suspected airway obstruction. The relatively low blood solubility of sevoflurane permits rapid equilibration between alveolar gas and arterial blood with consequently swift induction of anaesthesia after inhalation. Further, sevoflurane is non-pungent and well tolerated by patients. However, just as the onset of sevoflurane anaesthesia by inhalation is swift, so is its offset, and when alveolar ventilation is restricted, it may prove difficult to induce anaesthesia. In addition, when the supply of sevoflurane is discontinued during an intubation attempt, awakening will be swift. In contrast, the older agents, halothane and ether, would, once anaesthesia had been induced, permit a longer interruption of anaesthetic delivery without the risk of patient awakening.

Single-dose propofol without concomitant narcotic has been described for tracheal intubation. However, intubating conditions were inferior to those achieved when fentanyl was administered.\(^2\) Using larger doses of propofol probably causes haemodynamic depression; therefore, the technique cannot be recommended.

Propofol in combination with an opioid has been used by many investigators to facilitate neuromuscular blocking agent-free intubation. Logically, intubation should be attempted at or close to peak drug effect, which is in turn determined by the interaction between propofol and the opioid, and either remifentanil or alfentanil which are both characterized by swift equilibration between arterial blood and the effect site\(^3\) is suitable.\(^4 5\) In contrast, fentanyl

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**Editorial II**

**Tracheal intubation without neuromuscular blocking agents: is there any point?**

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4. Egan TD, Kern SE, Johnson KB, Pace NL. The pharmacokinetics and pharmacodynamics of propofol in a modified cyclodextrin formulation (Capsisol) versus propofol in a lipid formulation (Diprivan): an electroencephalographic and hemodynamic study in a porcine model. *Anesth Analg* 2003; 97: 72–9