Propofol

The Challenges of Formulation
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Propofol is a potent lipophilic anesthetic that was initially formulated in Cremophor EL for human use. Because of the occurrence of Cremophor EL anaphylaxis and improvements in the quality of lipid emulsions, it was ultimately brought to market as 1% propofol formulated in 10% soybean oil emulsion. Emulsions represent complex formulation compositions whose suitability for intravenous administration is dependent on a number of factors. Despite the success of propofol emulsions, drawbacks to such formulations include inherent emulsion instability, injection pain, a need for antimicrobial agents to prevent sepsis, and a concern of hyperlipidemia-related side effects. Efforts to overcome such drawbacks have involved the development of propofol emulsions with altered propofol and lipid contents, the addition of different excipients to emulsions for antimicrobial activity, and study of nonemulsion formulations including propofol–cyclodextrin and propofol–polymeric micelle formulations. In addition, a number of propofol prodrugs have been made and evaluated.

PROPOFOL (2,6-diisopropylphenol) has gained popularity as an agent for both induction and maintenance of anesthesia. This is primarily because of its rapid onset, short duration of action, and minimal side effects. Its use has expanded from solely an anesthetic agent to a sedative–hypnotic agent used in the intensive care unit and in outpatient procedures. The anesthetic properties of 2,6-diisopropylphenol were initially reported in January 1973 by ICI (coded as ICI 35868) in Cheshire, England. The first clinical trials were conducted in Europe in 1977 using a 1% preparation formulated in Cremophor EL, but this formulation was not clinically tested in the United States. High incidences of anaphylaxis with the Cremophor EL formulation prompted its withdrawal from development.

Propofol in an oil-in-water or lipid-based emulsion was evaluated in clinical trials in Europe in 1983 and in the United States in 1984. Its anesthetic properties were found to be similar to the Cremophor EL formulation, but without the anaphylactic reactions. Propofol in lipid emulsion was subsequently launched in the United Kingdom and New Zealand in 1986 and in the United States in November 1989. It was discovered that ethylenediaminetetraacetic acid (EDTA) had antimicrobial activity in emulsions, and in 1996, EDTA was added to propofol emulsion for the U.S. market. In 1999, a generic formulation containing sodium metabisulfite as the antimicrobial agent was also introduced to the U.S. market.

The ability to formulate propofol in a biocompatible vehicle having minimal side effects and appropriate pharmacodynamic profiles is critical to the use of propofol as an intravenous agent. This is a particular challenge for propofol because of its high lipophilicity. Despite the market success of propofol emulsions, there continue to be drawbacks associated with the current formulations. These include, emulsion instability, need for antimicrobial agents, hyperlipidemia, and pain upon injection. In addition, questions remain about specific excipients added to the emulsions to inhibit microbe growth. The fact that propofol is an excellent anesthetic and sedative but is not supplied in what can be considered an ideal vehicle has spawned efforts to find improved formulations for this compound. The objective of this review is to provide a background on propofol formulations, highlight clinical implications of each, and discuss newer efforts to reformulate propofol.

Propofol Chemistry

Propofol is a unique compound compared to the other intravenous anesthetics. It is a simple phenol substituted with two isopropyl groups in each of the positions adjacent to the hydroxyl group, the ortho positions (fig. 1). In its pure form at room temperature, it is an oil with a slightly yellowish color, but it freezes at only 19°C. Although most intravenous anesthetics can be administered as aqueous salts, propofol cannot be. Its lone ionizable functional group, the hydroxyl, has a pKₐ of 11, which renders it unsuitable for forming salts in solu-
The remaining portion of the molecule, the benzene ring and isopropyl side groups, are highly lipophilic. The result is a molecule with a poor water miscibility (150 µg/l). This high lipophilicity (logP = 4.16) means that good propofol miscibility can only be achieved in lipophilic substances or organic solvents. Because vehicles for clinical delivery of anesthetics should be devoid of sedative and anesthetic properties, as well as toxic side effects, nearly all small-molecular-weight organic solvents into which propofol is freely miscible are not useful.

Propofol Formulations

Cremophor EL

The purpose of a vehicle for an intravenous drug is to evenly disperse the active ingredient in a suitable volume that allows the clinician to administer the drug in a convenient dose size while not inducing side effects that are too great. A requirement for maintaining highly lipophilic substances dispersed in an aqueous solution is for the formulation to contain additional substances, emulsifiers or surfactants, that facilitate dispersion of the drug molecule within the aqueous phase. Discovery of the anesthetic effects of propofol in the ICI labs of James Glen involved the screening and synthesis of a large array of related alkyl-substituted phenol compounds. In the initial animal studies, propofol was chosen to be administered in mixtures of the common drug surfactant, Cremophor EL, and water, where the Cremophor EL concentrations ranged from 10 to 16%. The first human trials of propofol were performed using a formulation of 2% propofol, 16% Cremophor EL, and 8% ethanol (written personal communication, John B. Glen, Ph.D., Glen Pharma Ltd., Knutsford, Cheshire, United Kingdom, October 27, 2004). The reason for the 2% formulation was that the potency of propofol was initially underestimated. Ethanol was included in the 2% solution to eliminate cloudiness. It was subsequently determined that 1% was a suitable concentration for anesthesia, and this lower propofol concentration in Cremophor EL (16%) did not require ethanol for clarification. Clinically, propofol injection in Cremophor EL was found to cause significant pain upon injection. The 1% formulation without ethanol was less painful upon injection. Consequently, initial development of propofol continued with the Cremophor EL-based vehicle. Clinical trials were conducted in Europe (1977–1981) using 1% propofol in 16% Cremophor, and more than 1,000 patients were studied.

The perceived suitability of Cremophor EL as a vehicle for propofol was largely based on its previous use as a vehicle for propanidid (Epontol®, Bayer AG, Leverkusen, Germany) and the anesthetic steroids alphaxalone and alphadolone (Althesin®, Glaxo Laboratories Ltd., Greenford, Middlesex, England). Cremophor EL is a nonionic surfactant synthesized by the polyethoxylation of castor oil (fig. 2). Its synthesis is accomplished by the treatment of castor oil with ethylene oxide, a process that yields a family of polyethoxylated compounds. Castor oil contains approximately 87% ricinoleic acid, CH₂(CH₂)₅CH(OH)CH(CH₂)₇COOH. Consequently, the major component of Cremophor EL is polyoxyethyleneglyceroltriricinoleate.

Cremophor EL has a critical micellar concentration of approximately 0.009%. When mixed with water in all but the most dilute concentrations, it aggregates into micelles (micellar phase). The size of such micelles are small (< 100 nm), allowing most visible light (390–750 nm) to pass though the solution, giving it a transparent appearance. Propofol in such micellar solutions predominantly resides in the hydrophobic core of the micelle from which it diffuses after administration. Studies of paclitaxel, another lipophilic drug formulated in Cremophor, have shown that after injection, the micelles in part function to slow the release of free drug.

The well-known adverse reactions to propofol/Cremophor EL injections are characterized by histamine re-
lease, complement activation, and severe hypersensitivity reactions.\textsuperscript{6,28,29} As noted, the elimination of ethanol from the original formulation lessened pain upon injection; however, pain continued to occur in propofol/Cremophor EL injections.\textsuperscript{4} \textit{In vivo}, Cremophor EL is degraded by serum esterases and releases ricinoleic acid in the bloodstream.\textsuperscript{22} Because of this, Cremophor EL infusion can cause hyperlipidemia. For example, intravenous infusion of 0.5 ml/kg Cremophor EL to dogs resulted in increases in serum lipids, lipoprotein patterns, and tissue lipid content.\textsuperscript{30} In addition to these effects, Cremophor EL can cause a peripheral neuropathy.\textsuperscript{22} These problems, particularly the anaphylactic reactions, were ultimately attributed to Cremophor EL. This was confirmed by the anaphylactic reactions to the Cremophor–propanidid and Cremophor–Althesin\textsuperscript{®} formulations, which caused them to be withdrawn from the market.\textsuperscript{31,32}

\textbf{Lipid Emulsion}

Other formulations were also considered for propofol during its initial development around 1977. These included lipid-based emulsions, Tween and Mulgofens surfactants, and some poloxamers (written personal communication, John B. Glen, Ph.D., October 27, 2004). The first lipid emulsions examined were not satisfactory because the onset of anesthesia was delayed, potency was lost, and duration of anesthesia was prolonged compared with propofol formulated in Cremophor EL. Tween and Mulgofens generally produced histamine release in dogs and pigs and were not pursued. The poloxamers studied exhibited toxicologic problems and were not given to humans.

In the early 1980s, emulsion technology had improved to the point that propofol emulsions could be made that were stable and had the droplet sizes that maintained the anesthetic properties of propofol. This reformulation represented a significant improvement in intravenous propofol formulation and is the current mainstay of propofol delivery. Although injection pain remained a problem, propofol in a lipid emulsion formulation was found not to cause anaphylactic reactions, and it resulted in good pharmacodynamic characteristics. Emulsions with differing oils, e.g., safflower and cotton oil, and with different emulsifiers were investigated. However, the emulsion formulation ultimately chosen for development was one having the same components as the parenteral fat formulation, Intralipid\textsuperscript{®} (Kabi/Pfrimmer, Munich, Germany), \textit{i.e.}, soybean oil (100 mg/ml), egg yolk lecithin (12 mg/ml), and glycerol (22.5 mg/ml).\textsuperscript{53} Each component performs a specific function in forming the ultimate formulation. Soybean oil holds the bulk of the propofol in a medium that can be stabilized and dispersed; lecithin serves as an emulsifier to stabilize the small propofol–soybean oil droplets in aqueous dispersion, and glycerol maintains the formulation isotonic with blood.\textsuperscript{54} The pH of the emulsion is adjusted with the base, sodium hydroxide, to around 7.0–8.5 for optimal emulsion stability. In such a formulation, propofol is highly concentrated in the emulsified oil droplets (defined as the discontinuous phase), with only small quantities in the aqueous phase (\textit{i.e.}, continuous phase), the latter of which constitutes the largest volume of the emulsion.

Upon administration of a propofol-containing emulsion, propofol diffuses across the droplet interface and passes into the bloodstream. Major factors that govern this process for propofol or any lipophilic drug are the drug concentration gradient, the partition coefficient, the drug diffusivity in both phases, and the interfacial area of the drug-containing oil droplets.\textsuperscript{35} Therefore, similar to any drug releasing particle, emulsions slow the availability of free drug as compared with drugs administered in solutions in which they are molecularly dissolved. The total interfacial surface area is a highly important factor in the rate of drug release from a drug-containing droplet. This in turn is dependent on the size and number of oil droplets resulting from the injection. In a propofol emulsion with the contents noted above (10% fat emulsion), oil droplet size is a significant factor. If it were to contain uniform droplets (monodisperse) of 1.0 \(\mu\text{m}\) in diameter, the total oil–water surface area, or droplet–aqueous phase interface, would be 0.66 m\(^2\)/ml. However, if the particle size were reduced to 0.1 \(\mu\text{m}\), it would have a total oil–water surface area of 27.6 m\(^2\)/ml, nearly 42 times greater.\textsuperscript{35} The latter allows for a more rapid rate of release of propofol to the blood.

Studies of propofol anesthesia in rats demonstrated that propofol emulsion formulations have distinct clinical advantages. Dutta and Ebling\textsuperscript{56,57} showed that propofol administered in lipid emulsion was more potent and rapid acting than equivalent doses of propofol administered by a method involving a lipid-free vehicle. Propofol emulsion administration resulted in a smaller propofol volume of distribution and shorter times to peak electroencephalographic activity at onset, loss of righting reflex, and maximal electroencephalographic effects as compared with propofol administered in the lipid-free vehicle.\textsuperscript{56} It was not clarified as to whether this method delivers molecularly dissolved propofol or in part propofol droplets. Co-administration of propofol in this lipid-free vehicle with a lipid emulsion containing no propofol provided evidence that propofol needed to be incorporated into the emulsion soybean oil droplets for the better pharmacodynamic profile. The finding that lung concentrations of propofol were significantly higher after the administration of the propofol in the lipid-free formulation compared with the emulsion formulation led the authors to hypothesize that the emulsion formulation protected propofol from a high first-pass sequestration by the lung, possibly by maintaining more propofol in the central vascular space.\textsuperscript{58} Compar-
ison of the pharmacokinetic-pharmacodynamic parameters of propofol emulsion and propofol in 10% Cremophor EL did not show large differences, but there was a trend of the propofol emulsion being more potent than propofol in Cremophor EL.39

**Emulsion Droplet Size**

Emulsions are not composed of stable uniform molecular structures but of emulsified oil droplets whose integrity is dependent on a number of interactive forces. A major consideration in preparing emulsions for intravenous administration is to manufacture them such that the emulsified oil droplets are sufficiently small so that they can pass through capillaries (5–7 μm) without causing emboli. The optimal size is generally considered less than 1 μm.40 Second, they need to be sufficiently small so that they rapidly release the drug. Furthermore, emulsions need to have a great enough physical stability to withstand heat sterilization and maintain their integrity for their prescribed shelf life. Propofol emulsions have an expiration date of 2 yr after manufacture and a specified storage temperature range of 4°–22°C.18

Propofol emulsion and other emulsions for intravenous delivery are manufactured so that the oil droplets average 0.15–0.3 μm (150–300 nm).41,42 These sizes are similar to naturally occurring chylomicrons. In general, emulsions with droplets of 0.1–100 μm are known as macroemulsions, whereas emulsions with droplets of smaller size (< 0.1 μm, or 100 nm) are known as microemulsions.43 Microemulsion formation typically requires the presence of additional coemulsifiers (or cosurfactants), and they tend to form spontaneously. Macroemulsions require vigorous mixing to manufacture. Propofol and similar emulsions with droplet sizes smaller than 1 μm are created using multistage, high-shear homogenizers.43–45 Subsequent sterilization is usually done by autoclaving, although filtration is possible given the small droplet sizes relative to that of microbes.

The visible appearance of propofol and other emulsions as white milky solutions results from the property of small particles, but those that are large relative to the wavelength of white light, to reflect and refract light in a regular manner when dispersed.26 Particles less than approximately 0.01 μm, the size range of some micelles, including Cremophor EL micelles, as noted are transparent because they allow nearly all light to pass through.26 A number of analytical techniques have been developed for measuring particle sizes. These include laser light scattering, Coulter counter, ultrasonic spectroscopy, and microscopy.41,46,47 Laser light scattering can be used to measure particle sizes in micellar solutions as well as the larger macroemulsions.

**Emulsion Droplet Stability**

Obtaining long-term droplet stability is a major challenge in developing commercial emulsions for intravenous administration. Micelle-containing formulations, such as propofol in Cremophor EL, are thermodynamically stable and remain intact for indefinite periods.43 Microemulsions are likewise thought to be highly stable. Oil-in-water macroemulsions, however, are thermodynamically unstable. The lowest energy state of a mixture of emulsion components is represented by two completely separated phases, an upper layer of oil and a lower layer of water. The critical emulsion component that allows for small oil droplets to be dispersed in the water phase with relatively good stability is the emulsifier. The emulsifier reduces the interfacial tension between an oil and water and allows the oil to form stable dispersed droplets (discontinuous phase) within the water phase (continuous phase). Emulsions in reality begin...
to degrade upon manufacture, at very low rates if stored as recommended and at more rapid rates if handled and stored outside the manufacturer’s recommendations. When properly handled, emulsions should remain acceptable for administration before their expiration date.

An emulsion’s ultimate stability is derived from several forces, the formation of a mechanical barrier between the oil droplets and aqueous phase, and electrostatic repulsive forces between droplets. Disruption of these stabilizing forces will cause the emulsion to degrade, the end result being separation of the oil phase from the aqueous phase. The major emulsifier components in egg yolk lecithin, phosphatidylcholine and phosphatidylethanolamine, consist of lipophilic side chains (esterified fatty acids) bound to polar heads at one end (fig. 4). These molecules bridge the interface between the dispersed oil droplets and water. The oil-miscible side chains interact with the soybean oil, and the polar head interacts with the aqueous phase. The phosphates and nitrogen-containing moieties are charged (negative for phosphate and positive for the choline nitrogen) and confer a polar character to the head group, allowing aqueous interactions that form a mechanical barrier.

The negative electrostatic repulsive forces are derived from small quantities of free fatty acids and phosphatidic acids in egg yolk lecithin. In early studies, it was found that pure phosphatidylcholine was a poor emulsifier compared with mixtures of phospholipids that occur naturally. Naturally occurring egg yolk lecithin contains in addition to phosphatidylcholine and phosphatidylethanolamine, lysophosphatidylcholine, lysophosphatidylethanolamine, sphingomyelin, and phosphatidylinositol. These additional components were thought to facilitate the formation of the mechanical barrier, but it was determined that the predominant factor was the smaller quantities of free fatty acids and phosphatidic acids, which possess only negative charges. These free long-chain acids cause the emulsified oil droplets to possess a net negative electrostatic charge on their outer surfaces. The electrostatic charges impede droplet collisions and confers significantly greater emulsion stability.

The effective charge on emulsion oil droplets, thus a measure of emulsion stability, is characterized by its zeta potential. Zeta potential (ζ) is a measure of the sign (±) and magnitude of the surface charge and is determined by the electrophoretic mobility of the droplets, i.e., migration in an electrical field. The more negative the zeta potential is, the greater the net charge of the droplets is and the more stable the emulsion is. Emulsion droplets with zeta potentials of −40 to −50 mV are considered charged stabilized. Of note is that emul-

Fig. 4. Schematic of a soybean oil droplet emulsified with lecithin components.
sions release additional small quantities of free fatty acids during heat sterilization and after manufacture due to phospholipid and soybean oil hydrolysis. Therefore, autoclaving can confer a greater stability to the emulsion. However, accompanying fatty acid release is a decrease in pH that acts to destabilize the emulsion.52 Because propofol emulsions are nonbuffered and pH can decrease over time, a pH range, rather than a specific pH, is listed on the product label.

Emulsion degradation has been studied by many investigators.47,50,53–55 Emulsion degradation can be described as occurring in several sequential processes (fig. 5).46,56 Suspended oil droplets naturally collide from natural brownian motion or they collide from external agitation. Upon some collisions, attractive forces (van der Waal interactions) develop between droplets due to droplet surface imperfections. When attractive forces overcome the repulsive forces, droplets adhere to each other, a state called flocculation. In the flocculated state, the thin aqueous film between two adhered droplets can rupture causing the oil of the two droplets to combine, thus creating a larger but still emulsified droplet, a process termed coalescence. Continuing coalescence yields droplets of increasingly larger size, which have a greater tendency to rise toward the emulsion surface (creaming), which in turn causes an increase in frequency of droplet collision. Last, droplets become sufficiently large so that free oil is formed on the surface of the emulsion, a process called cracking. Flocculation and creaming are the only reversible processes in emulsion degradation. After droplets coalesce and increase in size, they cannot be reduced in size except by rehomogenization. Because of the possibility of a small degree of creaming in commercial propofol emulsions, even in those within their shelf life, it is recommended that they be shaken by hand before use.18

The clinical significance of emulsion degradation is severalfold. Degradation can cause alterations in the release of propofol in vivo, e.g., decrease droplet surface area due to droplet enlargement. It may cause variations of propofol concentrations within a volume of emulsion due to creaming. Furthermore, it may lead to emboli upon emulsion intravenous administration because of presence of enlarged oil droplets or globules.

There are many factors that can facilitate emulsion degradation, physical and chemical. Major physical factors are increased temperature, agitation, and freeze–thawing.50,57 Major chemical factors include pH and the presence of electrolytes. Increased acidity and the presence of electrolytes, e.g., Na, K, Ca, Mg, Fe, destabilize emulsions by neutralizing the repulsive negative charges on the droplet surfaces.58 Changes in pH can also result in hydrolysis of the emulsifier. Lipid peroxidation, a generally slow process, can likewise result in emulsion destabilization by degrading the lipid emulsifier or droplet soybean oil.

Emulsion droplet size analysis can be represented as droplet size distribution curves because such emulsions are polydisperse (nonuniform droplet sizes). Even though propofol and other emulsions are manufactured so that the dispersed oil droplets average 0.15–0.3 μm in diameter, small populations of oil droplets do not fall within this range. Figure 6 shows droplet size distribution in two recently manufactured propofol emulsions.
and the same emulsions after they were subjected to stress by shaking and by freeze–thawing.\textsuperscript{50} Few droplets larger than 1 μm occur in the nonstressed emulsions. However, freeze–thawing and extensive shaking caused droplet enlargement. Freeze–thawing, however, is more detrimental to emulsions.

As noted in figure 6, emulsion droplet sizes can vary depending on manufacturing parameters, such as pH and excipient content. Sulfite-containing propofol emulsion as compared with EDTA-containing propofol emulsion have been found to contain larger oil droplets.\textsuperscript{59} This was attributed to the lower pH of sulfite-containing propofol emulsion (4.5–6.4 range) compared with nonsulfite-containing emulsions (7.0–8.5).\textsuperscript{41} Although detrimental to all emulsions, a single freeze–thawing process in the sulfite-containing propofol emulsion results in a large population of droplets larger than 6 μm in diameter (figs. 6 and 7). Frequently, free oil can be seen after freeze–thawing of emulsions.

**Propofol Emulsion Preservatives**

Antioxidants, per se, are not added to propofol emulsions to prevent drug oxidation. Propofol emulsions are manufactured and sealed under nitrogen atmospheres in the vials in which they are distributed.\textsuperscript{34} In addition, propofol itself functions as an antioxidant,\textsuperscript{50} and soybean oil naturally contains small quantities of the antioxidant, α-tocopherol (vitamin E).\textsuperscript{33} However, excipients are added to propofol emulsions to inhibit bacterial and yeast growth upon extrinsic contamination.\textsuperscript{4} A number of such excipients have appeared in the patent literature and are listed in table 1. However, only propofol emulsions containing disodium edetate (disodium ethylenediaminetetraacetate [EDTA]) or sodium metabisulfite are currently approved by the Food and Drug Administration for marketing in the United States.

**EDTA**

The impetus for adding microbe growth inhibitors to propofol emulsions occurred after the introduction of propofol to the U.S. market in 1990, when clusters of unexpected postoperative infections occurred in association with propofol use.\textsuperscript{4,10,61,62} Contamination was determined not to be related to inadequate sterility of propofol emulsion but to accidental extrinsic contamination.\textsuperscript{62} It was subsequently determined that 1% propofol emulsion without an antimicrobial agent supports the growth of several microorganisms, including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*.\textsuperscript{63–66} After this finding, the manufacturer of propofol emulsion, Zeneca Pharmaceuticals (now AstraZeneca Pharmaceuticals, Wilmington, DE) studied a number of additives. Ultimately, EDTA at a concentration of 0.005% (wt/vol) was selected.\textsuperscript{67} During

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**Fig. 7. Photomicrographs of EDTA-containing propofol emulsion (Diprivan®) (A–C) and metabisulfite-containing propofol emulsion (D–F) after a single freeze–thaw cycle. Reprinted from Han et al.,\textsuperscript{50} with permission from Elsevier.**
Table 1. Patented Propofol Emulsion Excipients

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the development of a microbe inhibitor–containing propofol emulsion, the Food and Drug Administration agreed that an additive to lessen the possibility of sepsis should be capable of retarding the growth of microbes in the emulsions to not greater than 1 log increase (10-fold) in 24 h after extrinsic contamination. That is, it should have microbe growth potential similar to a nonlipid infusion formulation, such as thiopental.62 EDTA at this low concentration was found not to affect the stability of the emulsion, propofol pharmacokinetics, or clinical profile of propofol.4,68,69 The addition of EDTA has virtually eliminated the occurrence of clusters of fever and infections associated with propofol emulsion use. However, aseptic precautions should be maintained during propofol emulsion administration.

EDTA is an ion-chelating agent that inhibits microbe growth by chelating vital trace metals.70 EDTA is water soluble; therefore, it predominantly resides in the aqueous phase of propofol emulsions. EDTA is used as a drug for emergency treatment of severe hypercalcemia and is potentially toxic at high concentrations. Infusion of propofol with and without EDTA to healthy patients aged 1 month to younger than 17 yr was associated with reduction in ionized calcium and ionized magnesium concentrations throughout the infusion period.69 Mild hypocalcemia (ionized calcium concentrations < 1.0 mmol/ml) was noted in one patient who received propofol without EDTA and in four patients who received propofol with EDTA. Neither clinical manifestations of hypocalcemia nor critical hypocalcemia (ionized calcium concentrations < 0.7 mmol/ml) were reported in this study.69 At the end of infusion, the mean (± SD) of EDTA concentration was 155.2 ± 64.5 ng/ml in the 36 patients who received propofol with EDTA.69 Ionized calcium concentrations were normalized in both groups 30 min after discontinuation of propofol infusion. In a more recent study, the same group of investigators found that the changes in ionized calcium and magnesium concentrations were similar in children younger than 3 yr, regardless of whether they received propofol (with EDTA) or sevoflurane anesthesia.71 Hypocalcemia seen during anesthesia and surgery is probably due to the stress of surgery,72 hyperventilation,73 or both.

**Sulfite**

Sulfite is added to the generic formulation of propofol in the form of sodium metabisulfite (Na2S2O5) at a concentration of 0.25 mg/ml.74 The purpose of added sulfite, similar to the addition of EDTA, is to inhibit microbe growth after the emulsion is unsealed and extrinsically contaminated. Sulfite differs from EDTA in its actions. It reacts with oxygen. This effect results in the oxidation of propofol. Propofol oxidation in sulfite-containing propofol emulsions involves the coupling of two propofol moieties, via propofol radical intermediates, to yield propofol dimer and propofol dimer quinone. Propofol dimer is a colorless compound, but propofol dimer quinone is yellow and is responsible for emulsion...
Propofol Emulsion Compatibility with Other Drugs

In view of the inherent instability and multiple forces stabilizing emulsions, it is not unexpected that emulsions mixed with other substances will facilitate their degradation.35,81 Mixture of aqueous lidocaine with propofol emulsion leads to such instability.82,83 Lilley et al.82 showed that the addition of lidocaine (0–50 mg) to 20 ml propofol emulsion progressively lessened the zeta potential of the droplets from −38 mV to +2 mV, the latter value occurring at 50 mg lidocaine added from a 2% solution. These investigators found that droplet sizes remained on average 0.19 μm (after 90 min at room temperature) with up to 10 mg lidocaine added. Above 10 mg lidocaine, droplet size increased. Masaki et al.85 used scanning electron microscopy to more definitively assess droplet size and found that droplet enlargement (3.6 μm mean diameter) occurred at 60 min when 40 mg lidocaine (2% solution) was mixed with 20 ml EDTA propofol emulsion. At 20 mg lidocaine, droplet enlargement (4.1 μm mean diameter) was noted at 24 h. All droplet enlargements were characterized by time-dependent increases. Scanning electron micrographs of a propofol emulsion droplet enlargement due to mixture with lidocaine solutions is shown in figure 8. This micrograph shows the presence of a droplet greater than 10 μm. The clinical implication is that mixing of 20 ml propofol (1% Diprivan®, AstraZeneca Pharmaceuticals LP, Wilmington, DE) and more than 20 mg lidocaine should best be avoided or used immediately after mixing.85

Propofol emulsion instability resulting from lidocaine may be attributed in part to an increase in acidity from the lidocaine solutions. As previously noted, hydrogen ions mask the repulsive negative charges on the droplet surfaces. An additional factor may be lidocaine itself. Lidocaine exists in a pH-dependent uncharged (lipophilic) form and a charged (aqueous) form.84 As such, it may interact with the emulsifier and aid in mechanical destabilization of the emulsion. Likewise, in its cationic form, it may also neutralize the negative surface charges.

Paw et al.85 studied mixtures of thiopental (2.5%) and propofol emulsion. These investigators found that in contrast to the effects of lidocaine, thiopental did not alter the zeta potential of the propofol oil droplets. Furthermore, mean droplet size remained similar between thiopental–propofol emulsion mixtures and propofol emulsion alone, i.e., 0.2 μm. Thiopental is formulated in base (pH 10.5); therefore, thiopental does not acidify propofol emulsions when mixed. Prankard and Jones86 also previously noted that thiopental did not cause a significant droplet enlargement.

Propofol emulsion mixed with other substances can also destabilize emulsions. One of note is the parenteral solution protamine. Lamontagne et al.87 reported that propofol emulsion administered via an intravenous line that had been previously used to infuse protamine sulfate resulted in rapid phase separation of the emulsion with the observation of large oil globules.88

Emulsion Droplet Size and Risk of Emboli

Fat globules of a sufficiently large size, usually those considered to be greater than 5–6 μm, are thought to put patients at risk for fat emboli.89,90 Kanke et al.89 studied the clearance of 14C-labeled polystyrene divinylbenzene microspheres in dogs and found that microspheres 7–12 μm in diameter were filtered mechanically and retained for long periods in the lung. Smaller microspheres, 3–5 μm, were found in the spleen and liver. Similarly, Illum et al.90 studied the clearance of polystyrene and cellulose particles in rabbits. These investigators found that these particles averaging 1.27 μm in diameter were taken up by the reticuloendothelial system of the liver, whereas 15.8-μm droplets were mechanically filtered in the lungs. Few studies have directly evaluated emboli caused by emulsified oil droplets. Although these studies relate particle size to filtration, it should be noted that the microspheres studied are rigid
particles, whereas emulsified oil droplets have an ability to deform.

However, Marmarou (written personal communication, Anthony Marmarou, Ph.D., Professor, Department of Surgery, Virginia Commonwealth University, Richmond, Virginia, December 8, 2003) compared oil localized in the brains of rats administered the commercial sulfite-containing propofol emulsion and in an EDTA-containing propofol emulsion. This was done by adding a lipophilic fluorescent dye (Nile red) to the emulsions to enable visualization of aggregated oil after injection. Microscopically visible aggregates of oil could be seen in the brains of rats given sulfite-containing propofol emulsion (fig. 9A) but not in the brains of those given EDTA-propofol emulsion (fig. 9B). This confirmed the studies of Han et al. and Driscoll that sulfite-containing propofol emulsion is less stable and showed that lipid aggregation can occur in vivo from emulsions having enlarged droplets. Furthermore, it suggests that not all enlarged oil droplets are filtered by the lungs. In view of these results, more study is needed to determine the effects of droplet enlargement and lipid aggregation on tissue perfusion from such infusions.

### Biochemical Fate of Oil Droplets

In addition to droplet size considerations, the infusion of propofol causes an increase in lipid in the bloodstream. It is believed that propofol-containing emulsified oil droplets meet the same fate as natural chylomicrons formed by the intestinal mucosal cells during absorption of dietary fat. Chylomicrons are 0.08- to 0.5-μm oil spheres encapsulated with phospholipid, cholesterol esters, and apolipoproteins. These oil droplets are transported to the blood system via lymph channels. Some natural chylomicrons are taken up without metabolism by organ tissues, including adipose tissue, cardiac muscle, and mammary glands. Others, upon entering the bloodstream, undergo triglyceride hydrolysis in the capillaries by lipoprotein lipase to release free fatty acids. In the latter case, the chylomicrons shrink in size, and their remnants are removed by the liver.

Upon the injection of Intralipid® or propofol emulsion, the oil droplets, which initially have no proteins bound to them and do not contain cholesterol esters as do natural chylomicrons, acquire proteins in the bloodstream. The proteins acquired include apolipoproteins, including apolipoprotein CII (apo CII) and apolipoprotein E (apo E). As occurs with natural chylomicrons, some of these oil–lecithin–lipoprotein complexes are taken up by body tissues, and others attach to the capillary endothelial tissue in association with lipoprotein lipase. The triglycerides then become partially hydrolyzed releasing free fatty acids. The free fatty acids are taken up by the cells for metabolism and some become albumin bound in the circulation. This continued activity causes the emulsified oil droplets to lose triglyceride, shrink, and become triglyceride-poor. The triglyceride-poor droplets, or remnants, are then taken up by the liver and degraded by endocytosis. Although the reticuloendothelial system is important for the clearance of many particles, it does not seem to be the major pathway for clearance of chylomicrons or Intralipid® droplets. Only small quantities of these droplets are found in the spleen.

The fatty acids contained in soybean oil triglycerides administered to the body are predominantly linoleic (18:2, 54%), linolenic (18:3, 7.8%), stearic (18:0, 2.9%), and oleic acids (18:1, 26.4%). Because of these chain lengths, soybean oil is known as being composed of long-chain triglycerides (LCTs, 12–22 carbons). Some additional free fatty acids originate from those in the egg, such as arachidonic acid (20:4, 2.1%) and eicosapentaenoic acid (20:5, 0.9%).

Fig. 9. Soybean oil aggregation in the brains of rats given sulfite-containing propofol (A) and EDTA-containing propofol (B). Nile red (5 μg/10 ml) was added to sulfite-containing and EDTA-containing propofol emulsions. Each emulsion was infused at a rate of 60 mg • kg⁻¹ • h⁻¹ to each rat for 4 h. After infusion, brain tissue was obtained and sectioned into 20-μm slices. Visualization was performed the same day with a Nikon fluorescent microscope (Carrollton, TX) (200×, BA 600-660, G-2/E/ TRITC), using a SPOT Imaging System and Software (Diagnostic Instruments, Inc.). From Driscoll et al. 91; reproduced with permission.
yolk lecithin, the major ones being palmitic (16:0, 32.5%), oleic (32%), stearic (15.7%), linoleic (11.3%), linolenic (0.3%), and arachidonic (0.2%).

Studies of Intralipid® droplets, which are phospholipid-rich compared with natural chylomicrons, demonstrate that they are cleared more slowly than natural chylomicrons. Evaluation of emulsions containing different triglycerides showed that the nature of the oil can alter the clearance rates and clearance pathway. For example, omega-3 fatty acid–containing emulsified oil droplets are less dependent on lipoprotein lipase and are cleared faster than Intralipid® oil droplets by extrahepatic tissues. With emulsions containing mixed LCT (soybean oil) and medium-chain triglycerides (MCT), plasma free fatty acid concentrations increase faster than LCT alone, suggesting that different rates of hydrolysis occur. Particle size is also a variable in clearance. In general, larger particles are cleared faster than smaller particles.

It is unclear whether propofol-containing Intralipid® droplets are cleared differently or at different rates compared with Intralipid® droplets that do not contain propofol. Furthermore, whether clearance rates and different pathways of clearance, e.g., lipoprotein lipase versus tissue clearance, of different droplets affect propofol anesthesia has not been clarified.

Side Effects: Hyperlipidemia and Pancreatitis

A number of studies have addressed the occurrence of hyperlipidemia upon infusion of propofol emulsion, particularly in long-term infusions. Total lipid added by propofol infusion even at high doses is less than the maximum recommended fat intake per day (2.5 g · kg⁻¹ · day⁻¹). Most reports of plasma lipid concentrations after propofol emulsion administration are consistent with this low amount of lipid. Myles et al. showed that there was no change in plasma triglycerides in 22 cardiac surgical patients anesthetized with propofol and followed up for 4 h. There was a decrease in choleseterol and high-density lipoprotein, however. On the other hand, Eddleston and Shelly reported that a patient given a 10-day continuous propofol infusion had serum triglyceride concentrations four times normal, and they remained increased 72 h after termination of infusion. Mateu and Barrachina reported that of 12 critically ill patients given propofol (24–94 h, 3–8 mg · kg⁻¹ · h⁻¹), 5 exhibited hypertriglyceridemia that could be attributed to propofol emulsion infusion.

Prolonged infusion of high doses of propofol for sedation to critically ill children has been associated with a life-threatening syndrome, frequently referred to as propofol infusion syndrome. This is characterized by metabolic acidosis, multiorgan failure, lipemia, hepato-megaly, rhabdomyolysis, and death. For that reason, propofol is not recommended for sedation in pediatric intensive care unit patients. It is believed that the syndrome is caused by an effect of propofol to impair free fatty acid metabolism by inhibition of free fatty acid entry into the mitochondria. Critical analysis of this syndrome by Hatch and others indicates that the actual risk of this syndrome is low. Propofol infusion at a dose of approximately 50 µg · kg⁻¹ · min⁻¹ has been used safely for sedation of 142 critically ill infants and children. It has been suggested that the propofol infusion should be less than 75 µg · kg⁻¹ · min⁻¹ when used to sedate critically ill children and duration of infusion should be limited to 24 h. There is no clear evidence to establish a relation between propofol administration and pancreatitis. Some investigators recommended that blood should be tested for the presence of triglycerides, lactic acidosis, or lipemia. Randomized controlled trials evaluating the safety of propofol and investigating the mechanism of this toxicity are needed.

The association between propofol administration and pancreatitis remains obscure and is based only on a number of case reports. In some of these reports, pancreatitis developed after induction of anesthesia with propofol in healthy patients who had no risk factors for pancreatitis. In one patient, propofol was shown to cause a recurrence of pancreatitis. Kumar et al. pointed out that there are 25 reported cases of pancreatitis associated with propofol in the federal drug administration registry. Pancreatitis is common among patients with primary or secondary hypertriglyceridemia. The mechanism for propofol-induced pancreatitis is largely unknown, but hypertriglyceridemia and defects in lipid metabolism have been proposed. Gottardis et al. found no significant difference in serum lipid concentrations between patients who received a continuous propofol infusion for 3 days and those who received conventional sedation. In contrast, others reported hypertriglyceridemia in patients who received propofol for postoperative sedation for durations ranging from more than 24 h to 7 days.

Alternate Propofol Emulsion Formulations

Attempts to overcome the drawbacks of lipid infusion, pain, and potential for sepsis have been made by modifying phospholipid-emulsified propofol emulsions. Such modifications have included increasing propofol concentrations in the emulsion, creating emulsions containing less than 10% oil, creating emulsions having oils with different fatty acid contents, and modifying emulsion

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droplets with protein. Investigation of emulsions with novel surfactants is another potential direction for formulation improvement, but this approach is less favored because of the added burden of having to prove the harmlessness of each new emulsifier. Hemolysis, for example, is an inherent problem with many surfactants.45

A low oil emulsion that has been clinically evaluated is Ampofol® (Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, CA). Ampofol® is a 1% propofol emulsion containing 5% soybean oil and 0.6% lecithin, compared with 10% and 1.2%, respectively, in Diprivan®.120 In addition to the administration of less triglyceride per dose of propofol (LCTs, soybean oil), this formulation is thought to be less supportive of microbe growth121 because of the higher propofol-to-lipid ratio. Ampofol® was found to have similar pharmacokinetic profiles as propofol in 10% soybean oil emulsion. However, the incidences of mild and moderate pain were reported to be higher with this lower oil formulation than the 10% soybean oil emulsion.120,122 It is generally believed that the small quantity of propofol in the aqueous phase (18.57 μg/ml) of the 10% soybean oil emulsions is responsible for injection pain.123 Song et al.122 speculated that the increased incidence of pain from this 5% oil emulsion was the result of having less oil with which to sequester propofol from the aqueous phase.

Currently, two formulations that contain modified oil in the form of increased medium-chain triglycerides are IDD-D propofol (IDD-D = insoluble drug delivery; microdroplet; SkyePharma Inc., New York, NY) and Propofol-Lipuro® (B. Braun, Meslungen, Germany). Medium-chain fatty acids (MCTs) are those with hydrocarbon chains from 6 to 10 carbons long and are in high concentrations in coconut oil and palm kernel oil, for example. MCTs are more polar than long-chain triglycerides and have been used in previous drug emulsion formulations because of an increased ability to dissolve lipid soluble compounds.124 Furthermore, MCTs, as well as the fatty acids liberated, are metabolized more rapidly than LCTs94 and are better tolerated in both adults and neonates.125,126 A drawback to medium-chain triglyceride administration is formation of potentially toxic ketone bodies (acetoacetate and β-hydroxybutyrate).127 In addition, octanoate (8:0) liberated from such emulsions is potentially toxic.127

IDD-D propofol contains mixed LCTs and MCTs, the latter primarily consisting of caprylic (8:0) and capric (10:0) fatty acids, and a concentration of propofol of 2%. In a phase I study, anesthesia was induced with 2.5 mg/kg IDD-D propofol in volunteers and was maintained for 30 min in a subgroup of volunteers by an infusion at 0.2 mg·kg⁻¹·min⁻¹.128 The IDD-D propofol was found to have similar pharmacokinetics as 1% propofol in 10% soybean oil emulsion (Diprivan®).128 A previous study comparing a propofol emulsion having LCTs (Diprivan®) and mixed LCT/MCTs showed that this change in triglyceride content had little effect on propofol pharmacokinetics.129 Although the octanoate concentration (a metabolite of medium-chain triglycerides) returned almost to normal by 90 min after the termination of the infusion of IDD-D propofol,128 its safety is yet to be determined in a larger population of patients and after prolonged periods of infusion. On the other hand, the 2% propofol in an MCT emulsion (IDD-D propofol) showed greater pain upon injection and prolonged induction time than 1% propofol in 10% soybean oil emulsion (LCT).128 The increased incidence of pain upon injection with IDD-D propofol could be due to the greater total concentration of propofol in the MCT emulsion.

Propofol-Lipuro® (B. Braun) also contains mixed MCT-LCT and 1% propofol. It was reported that this formulation did not affect the pharmacokinetics or pharmacodynamics of propofol and was found to cause less pain upon injection in children and in adults.130–132 Theilen et al.133 studied a 2% propofol LCT emulsion (soybean oil) and a 2% propofol MCT–LCT (Propofol-Lipuro®) and found that patients given propofol MCT–LCT tended to have a more rapid triglyceride elimination.

Another medium-chain triglyceride formulation of 1% propofol (AM149; AMRAD Operations Pty. Ltd., Richmond, Victoria, Australia) has been developed.134 The specific content of this formulation is not clear; however, it is stated that it contains no soybean oil and contains ethyl oleate and dimyristoylphosphatidylglycerol as emulsifiers. The pharmacokinetic profiles, anesthetic properties, and cardiovascular effects were not different between LCTs (Diprivan®) and MCT (AM149) formulations.131,134 However, the medium-chain triglyceride formulation of 1% propofol was associated with significantly higher incidence of pain on injection (80%) and thrombophlebitis (93.3%) compared with the standard formulation (20% and 6.6%, respectively).134

Formulation of propofol in albumin-containing emulsions has also been investigated.135 This formulation involves a process that combines emulsified oil droplets, or propofol alone, and human serum albumin protein, resulting in an albumin-surrounded lipophilic phase.135 The mean size of such particles is typically in the range of 50–200 nm. This formulation involves a proprietary process that brings together the oil droplet and protein to form the nanoparticles. The presence of albumin alone is known to aid in stabilization of the emulsions by steric (or mechanical) effects as well as by electrostatic repulsions due to negatively charged albumin.136 Albumin-stabilized propofol emulsions containing reduced oil (<10%) or no oil have been tested in preclinical models showing similar anesthetic activity to propofol in 10% soybean oil emulsion (Diprivan®).137
solute. These structural features confer aqueous solubility on the cyclodextrin molecule while it is able to transport water-insoluble compounds. Ultimately, it is a complex interplay of intermolecular forces (van der Waals), including thermodynamic (hydrogen bonds) and solvent (hydrophobic) interactions that allow stable inclusion complexes to be formed.

Cyclodextrins of potential intravenous use are SBE4-β-cyclodextrins (sulfobutyl- cyclodextrins) and HP-β- cyclodextrins (hydroxypropyl- cyclodextrins). The parent cyclodextrins have limitations because of safety concerns. β-Cyclodextrin, for example, has shown to cause significant renal toxicity. Hemolysis is also a frequent problem with the high doses of cyclodextrins. Cyclodextrins are predominantly excreted in the urine unchanged. Pitha et al. showed that 90% of HP-β-cyclodextrin (hydroxypropyl-β-cyclodextrin) was excreted unchanged in the urine within 4 h. Frijlink et al. likewise showed that β-cyclodextrin at doses of 25–20 mg/kg was excreted in the urine unchanged in 24 h.

Studies of propofol-included cyclodextrins have used β-cyclodextrins. Propofol will complex to the 2-hydroxypropyl form of this cyclodextrin in a ratio of 1:1. It is hypothesized that propofol fits in the 2-hydroxypropyl β-cyclodextrin core where the protons of the aromatic ring and isopropyl groups are located inside the hydrophobic hydroxypropyl-β-cyclodextrin cavity, whereas the solvated hydroxyl group of propofol is located at the rim of the wider cavity (fig. 11). Sulfonylbutylether β-cyclodextrin has also been used to form inclusion complexes with propofol. Propofol-cyclodextrin formulations are clear solutions; they contain no oil, they are stable, and they require no special formulation methodologies. They may also be lyophilized and filter sterilized. Chemically, cyclodextrins are stable in base, but they are susceptible to hydrolysis in acid.

Pharmacodynamic studies of propofol-hydroxypropyl-β-cyclodextrin showed that in rats, this formulation caused a shorter induction time and longer sleep time in rats compared with propofol in emulsion. Egan et al. found that propofol sulfobutylether β-cyclodextrin formulation (Captisol®; CyDex Inc., Lenexa, KS) exhibited similar pharmacodynamic and pharmacokinetic effects to Diprivan® in a porcine model during a 3-h infusion. Whether the administration of propofol-cyclo...
dextrin formulations, particularly long term, will represent a toxicity risk is not clear. Of note is that Bielen et al. studied a propofol–hydroxypropyl-β-cyclodextrin (20%) formulation (5 mg/kg) in rats and found that a bolus dose caused a severe bradycardia and a significant decrease of blood pressure whereas hydroxypropyl-β-cyclodextrin alone did not. It has not been determined whether this is a general effect of propofol–cyclodextrin formulations. Another potential concern of cyclodextrins is that after release of the included drug, they may be able to bind coadministered lipophilic drugs. For example, rocuronium can strongly complex with various cyclodextrins, in particular sulfobutyl-β-cyclodextrin, and it substantially shortens the duration of action of this neuromuscular blocker.

Micelle Formulations

Early studies of poloxamers (trade names, Pluronics [BASF, Ludwigshafen, Germany] and Synperonics [Imperial Chemical Industries, London, United Kingdom]) for propofol delivery by Zeneca Pharmaceuticals involved Synperonic PE39/70 (Imperial Chemical Industries, Inc.), but it was ultimately not pursued. However, micelles made from other poloxamers have been given recent consideration for formulating propofol. Poloxamers consist of nonionic surfactants containing chains of polyethylene oxide, which form the outer shell of the micelle, and chains of polypropylene oxide, which form the inner hydrophobic core (fig. 12). These polyoxyethylene–polyoxypropylene compounds have both hydrophilic and hydrophobic components and form micelles when placed in aqueous solution in concentrations above their generally low critical micellar concentrations. Such polymeric micelles are small with particle diameters ranging in size from 20 to 80 nm, which, as noted for such small particles in solution, gives them a clear visual appearance. Rather than having a well-defined interface between the lipophilic component and water as in phospholipid emulsions, micelles have a more diffuse brush-like barrier of long ethylene oxide polymers, which becomes highly hydrated in solution. The hydrophilic brush border inhibits the attachment of these micelles to proteins. In contrast to phospholipid emulsions, such polymeric micelles are more dynamic structures which in solution continuously exchange unimers (isolated polymeric chains) between the micellar structure and the free polymers in solution.

Micelles consisting of mixed Pluronics have been shown to result in good propofol solubility. Pluronic 68 at a concentration of 10% wt/vol solubilizes propofol at a concentration of 0.8%. Pluronic 127 at 10% wt/vol solubilizes propofol up to a concentration of 1.7%. A mixture of P68/P127 micelles at a ratio of 7:3 solubilizes propofol up to 3.5–3.8%. The viscosity of these solutions is said to be similar to that of the current propofol oil-in-water emulsions. In vivo data from the administration of propofol in polymeric micelles has yet to be reported. An advantage of polymeric micelles, should they ultimately be used for human propofol delivery, include an ease of manufacture due to spontaneous micelle formation, inherent stability, unlike propofol phospholipid macroemulsions, and ease sterilization by filtration.

Propofol Prodrugs

Propofol prodrugs are compounds that will degrade, usually in the bloodstream, to release the propofol molecule. The primary objective of synthesizing propofol prodrugs is to create molecular entities that are soluble in aqueous phases and, where desired, slow the release of this anesthetic. A particular attraction of propofol prodrugs is that they have the potential to circumvent the complications of emulsion instability, lipid infusion, and the need for microbe growth inhibitors in the formulation. Several propofol prodrugs have been synthesized and have appeared in the patent literature. These include propofol hemisuccinate, propofol hemiglutarate, propofol hemiadipate, mono(propofol) phosphate, and di(propofol) phosphate. Altamore et al. have also described several cyclic amino acid esters of propofol. The carboxylic acid ester prodrugs are designed to be

Fig. 12. Structure of a Pluronic micelle composed of A-B-A polymers.

Fig. 13. Pathway of metabolism of the propofol prodrug, phosphono-O-methyl-2,6-diisopropylphenol (GPI 15715) by alkaline phosphatase.
hydrolyzed to release propofol, predominantly by the action of tissue esterases and to lesser degrees by non-enzymatic mechanisms.

Another propofol prodrug that has undergone significant study is phosphono-O-methyl-2,6-diisopropylpheno-
(n GI 15715, Aquavan® injection; Guilford Pharma-
ceuticals, Baltimore, MD). This compound undergoes hydrolysis by alkaline phosphatase rather than by ester-
as.\(^{158,159}\) It is hydrolyzed in the plasma to release free propofol, phosphate, and formaldehyde (fig. 13). Form-
aldehyde is both a critical endogenous metabolite as well as an exogenous toxin.\(^{160}\) One factor that distinguishes between the two the consequences seems to be formal-
dehyde concentrations. Although free formaldehyde has not been detected after GI 15715 administration in doses ranging from 290 to 1,160 mg over 10 min,\(^{161}\) formaldehyde is a reactive compound capable of binding to biologic constituents.\(^ {160}\)

A drawback of propofol prodrugs is that free propofol is dependent on the rate of molecular degradation of the prodrug in vivo. In fact, a study of GI 15715 in rats showed that as compared with Diprivan®, this prodrug exhibited a longer half-life, increased volume of distribution, delayed onset, and a longer duration of action.\(^{159}\) Such characteristics make it more suitable for long-term sedation than for anesthesia. Some propofol prodrug development in fact targets the use of propofol’s sub-
anesthetic effects, such as its antiinmigraine properties.\(^{162}\)

Conclusions

Propofol has clinical attributes that cause it to be a widely used anesthetic and sedative, but it is a difficult compound to formulate in stable aqueous vehicles suitable for routine clinical use. Propofol soybean oil emulsion formulations have met with considerable success, reasons being that they are largely composed of substances endogenous to the body, \(i.e.,\) triglycerides and phospholipids, and good emul-
sion droplet size and stability can be achieved when such emulsions are manufactured properly. The remaining con-
cerns with propofol emulsions, lipid infusion, pain upon injection, and need for antimicrobial agents, coupled with advances in formulation development, are driving research of new propofol formulations with improved attributes. Such efforts increasingly involve the use of more exoge-
nous substances and novel compounds of which thorough study must be done to ensure the greatest safety to the patient.

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