Fospropofol: Is there an infusion regimen for propofol equivalence?

Propofol is an intravenous (IV) sedative hypnotic which is commonly used as a bolus for the induction of general anesthesia. It is also used as an infusion for continuous sedation and as an adjunct for general anesthesia. The main advantage of propofol, as compared with other IV sedatives, is that it has an ultra-short half-life. This allows for a relatively rapid awakening.[1,2] Furthermore, propofol is devoid of the side effects of both nausea and vomiting. In addition, continuous low-dose infusions have been successfully utilized to treat recalcitrant nausea.[3]

Fospropofol is a water-soluble prodrug of propofol.[4,5] These two features give fospropofol clinical advantages, as well as disadvantages, with respect to propofol. Specifically, its water solubility allows it to be manufactured without egg lecithin, soy bean extract, or glycerol. Note that these are used as diluents with propofol. Furthermore, these additional ingredients may support microbial growth despite the presence of antimicrobial preservatives.[6-8] Moreover, administration of propofol to patients allergic to any of these additives is contraindicated. Hypertriglyceridemia, presumably from these diluents, has also been reported.[9,10] Of note, a lipid-free propofol formulation is currently being developed and investigated.[11]

Additionally, the current preparation of propofol produces pain on injection. This frequently requires the concomitant use of such medications as lidocaine, or ketamine, as analgesics.[12-15] It should be noted that ketamine has both local and general anesthetic properties.

In addition, propofol is lipophilic and is prepared as an emulsion. Thus, prolonged storage can lead to separation or "cracking" of the emulsion.[16,17] Propofol is also difficult to manufacture and numerous recalls, as well as shortages, of this drug have occurred.[18]

As shown in Figure 1, propofol is based upon phenol, with the addition of two isopropyl side chains, which are located at positions 2 and 6.

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However, fospropofol, as shown in Figure 2, is a water-soluble salt which utilizes phosphate and sodium ions.

Since fospropofol is a prodrug, a delay in peak onset occurs following the administration of a single dose. Using a 10 mg/kg IV bolus, the median time to sedation was reported as approximately 7 minutes with a range of 1 to 15 minutes.[4] This is in contradistinction to propofol which has a near-immediate effect.[2] Because of this, propofol is frequently used for rapid-sequence induction of general anesthesia, whereas this would not be possible with fospropofol. Furthermore, the time to awakening with fospropofol was reported within a range of 21 to 45 minutes; although still short, this is significantly longer than propofol.[4] Somewhat similar dose-response and pharmacodynamic properties have been reported in other

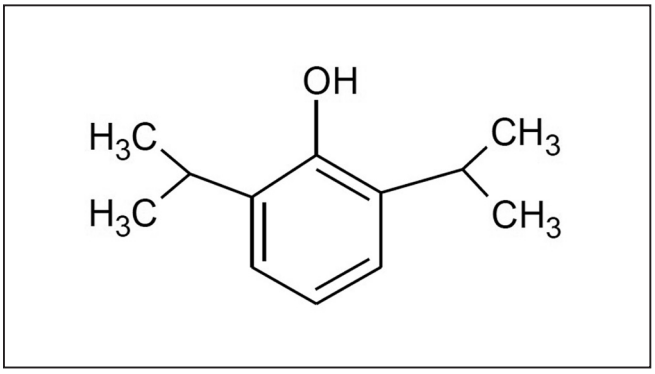

Figure 1: The lipophilic chemical structure of propofol

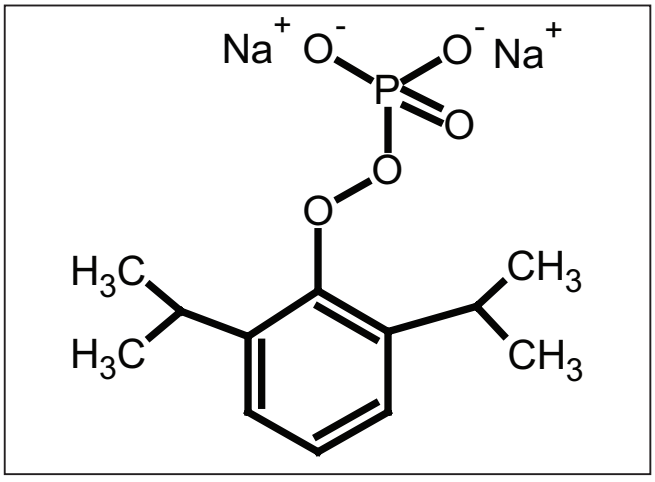

Figure 2: Fospropofol is a disodium-phosphate water-soluble salt which is enzymatically degraded to propofol by alkaline phosphatases

clinical studies.[19,20] In addition, the major side effects of fospropofol are pruritus as well as paresthesias. These are transient.[4,18-21]

Alkaline phosphatases enzymatically degrade fospropofol to propofol, with formaldehyde, formate, and phosphate produced as metabolic byproducts.[4] These are illustrated in Figure 3. Of note, formate is the anion of formic acid which is responsible for the itching produced from insect venom. This may explain fospropofol's side effect of pruritus. However, the resultant blood formaldehyde levels are not considered clinically significant.

Currently, fospropofol is only administered in intermittent IV boluses. However, a continuous infusion of this drug would result in a more stable level of sedation. Furthermore, the potential for excessive propofol levels from an IV bolus may be reduced with a carefully administered continuous infusion. Lastly, the use of syringe pumps, or other similar technology, would be more convenient than repetitive bolus administration.

To accomplish this, a "target dose" of propofol from the administration of fospropofol would need to be determined. This would result from a "propofol equivalent" regimen of fospropofol dosing. An understanding of the *gram-molar relationship* between fospropofol and propofol is therefore necessary. *Explicitly, one mole of fospropofol produces one mole of propofol.*[4] This is in contradistinction to an "approximate milligram equivalence" which is typically used when comparing similar-acting medications. Furthermore, equimolar dosing is frequently utilized when establishing bioequivalence.[22]

Thus, the number of moles for a given amount of drug is a direct representation of its associated number of molecules. To further illustrate the concept of equimolar dosing, the number of moles of propofol produced from an infusion of 100 mg/(kg·min), is:[23]

$$\frac{100\frac{\mu g}{(kg\cdot min)}}{(10^6\frac{\mu g}{g})\cdot(178.27\frac{g}{mol})}=\frac{100\frac{\mu g}{(kg\cdot min)}}{1.78\cdot10^8\frac{\mu g}{mol}}=5.61\cdot10^{-7}\frac{mol}{(kg\cdot min)} \quad (1)$$

Note that the molecular weight of propofol is 178.27 g/ mole. However, the molecular weight of fospropofol is 332.24 g/ mole. Based upon the molar dose from equation (1), the dose of fospropofol to produce an equimolar amount of propofol is as follows:

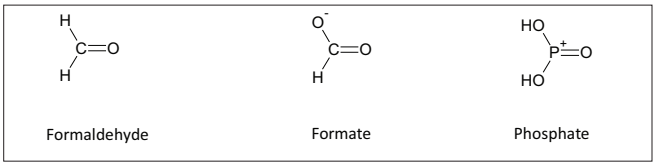

Figure 3: Formaldehyde, formate, and phosphate are also produced as fospropofol is metabolized

$$5.61\cdot10^{-7}\frac{mol}{(kg\cdot min)}\cdot(10^6\frac{\mu g}{g})\cdot(332.24\frac{g}{mol})=5.61\cdot10^{-7}\frac{mol}{(kg\cdot min)}\cdot(3.32\cdot10^8\frac{\mu g}{mol})=186\frac{\mu g}{(kg\cdot min)}\cdot \quad (2)$$

Thus, in terms of producing an equivalent number of moles of propofol:

$$186\frac{\mu g}{(kg\cdot min)}\text{ of fospropofol }=100\frac{\mu g}{(kg\cdot min)}\text{ of propofol} \quad (3)$$

Furthermore, the above ratio in equation (3) remains valid for other "target dosages" of propofol which would be produced from an infusion of fospropofol:

$$1.86.\ \frac{\mu g}{(kg\cdot min)}\{\text{target dose of propofol in }\}=\text{dose of fospropofol in }\frac{\mu g}{(kg\cdot min)} \quad (4)$$

It should also be noted that fospropofol is manufactured in a more concentrated form than propofol. Specifically, fospropofol has a concentration of 35 mg/ml, whereas the concentration of propofol is 10 mg/ml. Thus, the net flow rate for a fospropofol infusion is significantly less than that of an equimolar propofol infusion. This occurs despite the greater molecular weight of fospropofol.

As an example, for a propofol dose of 100 mg/(kg·min), the net flow rate, per kg body weight, is:

$$\frac{\left(100\frac{\mu g}{(kg\cdot min)}\right)\cdot\left(60\frac{min}{hr}\right)}{\left(10^6\frac{\mu g}{g}\right)\cdot\left(0.01\frac{g}{ml}\right)}=\frac{6\cdot10^3\frac{\mu g}{(kg\cdot hr)}}{10^4\frac{\mu g}{ml}}=0.6\frac{ml}{(kg\cdot hr)} \quad (5)$$

However, the flow rate per kg body weight for an equimolar dose of fospropofol is:

$$\frac{\left(186\frac{\mu g}{(kg\cdot min)}\right)\cdot\left(60\frac{min}{hr}\right)}{\left(10^6\frac{\mu g}{g}\right)\cdot\left(0.035\frac{g}{ml}\right)}=\frac{1.12\cdot10^4\frac{\mu g}{(kg\cdot hr)}}{3.5\cdot10^4\frac{\mu g}{ml}}=0.32\frac{ml}{(kg\cdot hr)} \quad (6)$$

Further research is necessary to clinically evaluate the benefits and limitations of a "propofol equivalent" dosing regimen of a continuous infusion of fospropofol. This would include blood levels of propofol, formaldehyde, phosphate, and formate which are produced from the metabolism of fospropofol.

Appendix: Numerical Examples

Example 1. It is desired to administer fospropofol based upon a molar equivalent of 90 $\frac{\mu g}{kg\cdot min}$ of propofol. Using Equation (4):

$$1.86(90\ \frac{\mu g}{(kg\cdot min)}\ \text{of propofol}) = 167.4\ \frac{\mu g}{(kg\cdot min)}\ \text{of fospropofol.} \quad (1A)$$

Based upon Equation (6), the associated flow rate per kg would be:

$$\frac{\left(167.4\frac{\mu g}{(kg\cdot min)}\right)\cdot\left(60\frac{min}{hr}\right)}{\left(10^6\frac{\mu g}{g}\right)\cdot\left(0.035\frac{g}{ml}\right)} = 0.287\ \frac{ml}{(kg\cdot hr)} \quad (2A)$$

For a 70 kg patient, this would correspond to a flow rate of:

$$\left(0.287\frac{ml}{(kg\cdot hr)}\right).\ (70\ kg) = 20.1\ \frac{ml}{hr}.$$

Example 2. It is desired to administer fospropofol using the molar equivalent of a propofol dose of $120\ \frac{\mu g}{(kg\cdot min)}$ 120. This would correspond to:

$$1.86.(120\ \frac{\mu g}{(kg\cdot min)}\ (120\ \text{of propofol}) = 223.2\ \frac{\mu g}{(kg\cdot min)}\ \text{of fospropofol.} \quad (3A)$$

Based upon Equation (6), the associated flow rate per kg would be:

$$\frac{\left(223.2\frac{\mu g}{(kg\cdot min)}\right)\cdot\left(60\frac{min}{hr}\right)}{\left(10^6\frac{\mu g}{g}\right)\cdot\left(0.035\frac{g}{ml}\right)} = 0.383\ \frac{ml}{(kg\cdot hr)}\ .(4A)$$

For a 70 kg patient, this would correspond to a flow rate of:

$$(0.383\ )\ \frac{ml}{(kg\cdot hr)}\cdot(70\ \text{kg}) = 26.8$$

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