Those acquainted with Hamlet will know the rest goes, “...ay, there’s the rub; For in that sleep of death what dreams may come?” That sleep of death...the King James Version of the Bible at times uses the word, “sleep” to mean death. So where am I going with this? What drug is in the news more than about any other these days? Yes, I am drinking the Kool Aid and joining the Michael Jackson hype. (For the young folks: “Kool Aid” is in reference to Jonestown, Guyana, another clever toxicological reference...look it up!) While at the time of this writing the toxicology results have not been released to the public, the not-so-secret-secret is that propofol will play a central role in Mr. Jackson’s death.

It is not my intention to impugn the reputation of a useful and effective drug like propofol. We all know that “dose makes the poison”, and propofol is just another one of those things that can be lethal if used incorrectly. So, what is this drug that the media is so hyped about?

History

While generic versions are available, propofol is marketed by AstraZeneca under the name Diprivan®. Diprivan® is not new; it was originally developed by Imperial Chemical Industries, now AstraZeneca, as ICI 35868 with clinical trials beginning in 1977. After a reformulation of the solublizing agent, due to anaphylactic reactions, it was re-introduced in 1986 as Diprivan®. Diprivan derives from a pseudo-acronym of the name DIisoPRopyl IntraVenous ANesthetic.

The goal of an anesthetic is to produce unconsciousness, immobility and amnesia. Some would argue that only amnesia and immobility are necessary since interoperative awareness is immaterial if it cannot be remembered; an interesting point. Be that as it may, propofol is quite efficient at producing amnesia in concentrations well below those required for immobility. As a result of this reputation and the fact that the propofol suspension is milk-like in appearance, it has been dubbed by many anesthesiologists as “milk of amnesia”. Unfortunately, this property would make propofol a prime candidate as a “date-rape” drug should it become more available to the public.
Analysis

Chemically propofol is the relatively simple molecule, 2,6-diisopropylphenol with a molecular weight of 178.27 amu and a pKa of 11.0. Propofol is readily extracted and detected in most acid/neutral extraction schemes. Due to its low molecular weight propofol elutes relatively early, however, and because of its sparse mass spectrum, consisting primarily of ions 163, 178, and 117, in order of descending abundance, propofol could be dismissed as a contaminant or artifactual peak, if an analyst were not expecting its presence. Due to its acidic proton, propofol can be easily derivatized by a wide variety of derivatizing reagents to yield higher ions, more amenable for mass spectrometry.

Pharmacodynamics/Pharmacokinetics

Propofol acts almost exclusively at the GABA receptor and has a volume of distribution of 2 – 12 L/Kg and a terminal half-life of 1.5 – 2.5 hours. Due to its high lipophilicity, propofol is rapidly partitioned to the tissues from the vascular space after the cessation of administration with an early distribution half-life of 7 -8 minutes.

Interpretative issues

The interpretation of postmortem blood propofol levels can be problematic. The literature reports that it requires a blood propofol concentration of 6 – 10 mg/L for anesthetic induction and concentrations of 2 – 4 mg/L for anesthetic maintenance, and that 50% of patients were awake and oriented after surgery at levels from 0.95 – 1.07 mg/L. However, Drummer reported in 1992 the case of a 29 year old female who committed suicide by intravenous injection of 400 mg of propofol. The decedent’s postmortem propofol concentration was 0.22 mg/L in femoral blood. In 5 other cases,
postmortem propofol concentrations ranged from 0.5 – 5.3 mg/L. This obvious overlap in lethal and subtherapeutic concentrations is undoubtedly due to its extreme lipophilicity and thus postmortem redistribution, especially in acute overdose situations. This is not unlike the conundrum faced by lethal injection opponents who seek to use low postmortem thiopental levels as evidence that the condemned was conscious at the time of the administration of the paralyzing agent and potassium chloride. (See StraightTox article on Lethal Injection.)

**Stability**

Further complicating the interpretation of propofol levels, is the fact that it has been shown that losses of propofol up to 36% are possible in whole blood stored at 4°C for 24 days. Agnieszka, et al. demonstrated a more rapid loss of propofol from whole blood stored at -20°C, dropping below the LOQ of 0.1 mg/L in as short as 20 days, as compared to whole blood stored at 4°C; these losses were not observed in plasma, however. It has also been demonstrated that intravenous solutions of propofol stored in plastic infusion bags have exhibited losses of 80% in 4 hours and 95% in 24 hours.

The above brings into question the role that plastic collection tubes, which are now seeing widespread hospital use, may play in the in-vitro stability of propofol, or thiopental for that matter.

Hmmm --- I feel a research project coming on.

**References**


Disposition of Toxic Drugs and Chemicals in Man, 7th Edition, Randall Baselt, Biomedical Publications, Foster City, CA
