Propofol introduced in USA in 1989 as a potent short acting intravenous sedative-hypnotic agent used to induce and maintain anesthesia in ICU. Propofol has a rapid onset of action (approximately 30 seconds), a rapid rate of distribution (half life 2-4 min) and a short elimination half life (30-60 minutes) and doesn't accumulate in patients with liver or kidney disease making it ideal in critically ill patients and used more common than any other sedative ***(Marik, 2004)*.**

Propofol has become widely accepted as a sedative agent in the ICU because of its favorable safety profile, rapid onset, and weaning characteristics, features that are important in populations who require frequent neurological assessment ***(Weber et al., 2003).***

The 2002 clinical practice guidelines for sedation and analgesia from the Society of Critical Care Medicine recommend propofol as the preferred sedative for mechanically ventilated patients when rapid awakening is important ***(Jacobi et al., 2003)*.**

Despite all of these advantages, propofol was associated with adverse drug related events. Propofol has a cardiovascular depressant effect that may lead to bradycardia and hypotension, particularly in volume depleted patients, respiratory depression, hypertriglyceridemia associated with

pancreatitis, pain with injection, green discoloration of urine, nausea, vomiting, and allergic complications have also been associated with propofol administration, in addition to the propofol related infusion syndrome (PRIS) ***(McKeage and Perry, 2003).***

In 1992, Parke et al published a landmark article that suggested a link between propofol infusions and mortality in children ***(Parke et al., 1992).***

Propofol related infusion syndrome (PRIS) has been defined as the abrupt onset of profound (typically refractory) bradycardia in the presence of lipemic plasma , a clinically enlarged liver or a fatty liver as observed at autopsy, metabolic acidosis with a base deficit more than 10 and / or muscular involvement with evidence of rhabdomyolysis or myoglobinuria ***(Bray, 1998).***

In 2006, Corbett et al documented a total of 15 adult cases of propofol infusion syndrome published in the English-language literature ***(Corbett et al., 2006).***

The true incidence of PRIS is unknown; however, Crozier on the basis of pooled clinical data calculated with a 95% probability that the incidence of PRIS is 1 in 270 patients (0.37%) or lower ***(Crozier, 2006).***

Among the documented cases of propofol related infusion syndrome, the associated mortality rate was 64%.

Since the syndrome was first described in 1992, the number of published case reports has increased 10 folds. However the true occurrence of the propofol related infusion syndrome is unknown because the number of patients who receive the propofol by continuous infusion on a yearly basis has not been reported ***(Wysowski and Pollock, 2006).***

So in this essay, we will discuss the detailed pharmacology of this drug and the pathophysiology of the propofol related infusion syndrome (PRIS) and how to suspect it early and how to manage it.

The aim of this essay is to discuss the propofol related infusion syndrome in critically ill patients. This essay will focus on the proposed pathophysiological mechanisms responsible for propofol toxicity and finally help clinicians in recognizing early warning signs and taking preventive measures in order to avoid full development of ‘propofol infusion syndrome’ that is associated with high mortality.

History:

Propofol (Diprivan) is the most frequently used intravenous anesthetic today. Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the development of 2, 6-di-isopropylphenol (propofol). The first clinical trial by Kay and Rolly reported in 1977, confirmed the potential of propofol as an anesthetic induction agent ***(Kay and Rolly, 1977).***

Propofol is insoluble in water and therefore was initially prepared with Cremophor EL. Because of anaphylactoid reactions associated with Cremophor EL in this early formulation of propofol, the drug was reformulated in an emulsion. Propofol has been used for induction and maintenance of anesthesia as well as for sedation ***(Laxenaire et al., 1992).***

Physicochemical characteristics:

Propofol is one of a group of alkylphenols that have hypnotic properties in animals. The alkylphenols are oils at room temperature and are insoluble in aqueous solution, but they are highly lipid soluble. The present formulation consists of 1 percent propofol (10 mg/mL), 10 percent soybean oil (100 mg/mL), 2.25 percent glycerol (22.5

mg/mL), 1.2 percent purified egg phosphatide (12 mg/mL). In the United States, disodium edetate (0.005%) was added as a retardant of bacterial growth. Propofol is available as a 1 percent solution in 20-mL clear glass ampoules, 50- and 100-mL vials. It is stable at room temperature and is not light sensitive. If a dilute solution of propofol is required, it is compatible with 5 percent dextrose in water ***(RxList, 2008).***

The diprivan emulsion is isotonic and has a pH of (7-8.5). Because propofol (Diprivan) solutions are emulsions, it is not surprising that it appears "milky" white as a result of light scattering ***(Dolin, 2000).***

Pain on injection occurs in 32–67% of patients when injected into small hand veins, but can be minimized by injection into larger veins and by prior administration of either 1% lidocaine or a potent opioid analgesic. Diluting the formulation with additional solvent (Intralipid) or changing the lipid carrier (Lipofundin) also reduced injection pain, probably due to a decrease in the concentration of free propofol in the aqueous phase of the emulsion. A new propofol formulation with sodium metabisulfite (instead of disodium edetate) as an antimicrobial has recently been shown to be associated with less pain on injection. However, the presence of the metabisulfite has raised concerns regarding its use in sulfite-allergic patients. Of

interest, a 2% formulation is available for long-term sedation to decrease the volume infused as well as the lipid load ***(Barash et al., 2001).***

Chemical description:

DIPRIVAN® (propofol) injectable emulsion is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2, 6-diisopropylphenol and has a molecular weight of 178.27. The structural and molecular formulas are described in **Figure (1).**

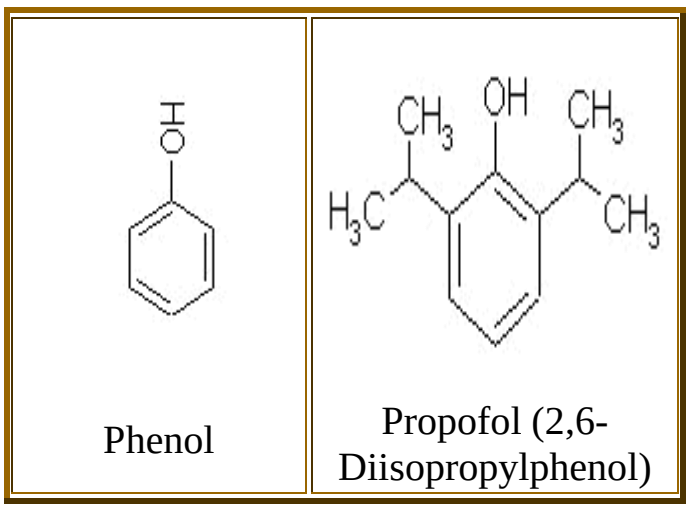

Fig. (1): Structural and molecular formulas of propofol ***(Katzung, 1998).***

Pharmacokinetics:

Distribution:

The pharmacokinetics of propofol are well described by multicompartment linear model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues. Following an IV bolus dose, there is rapid equilibration between the plasma and the brain, accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance. Distribution accounts for about half of this decline following a bolus of propofol. However, distribution is not constant over time, but decreases as body tissues equilibrate with plasma and become saturated. The rate at which equilibration occurs is a function of the rate and duration of the infusion. When equilibration occurs there is no longer a net transfer of propofol between tissues and plasma ***(RxList, 2008).***

What is Multicompartment Model?

The pharmacokinetics of propofol following a wide range of doses as well as following continuous infusions has been evaluated by numerous investigators, and it has been described by three-compartment models ***(Bailie et al., 1992).***

For many drugs, three distinct phases can be distinguished. There is a rapid "distribution" phase that begins immediately after the bolus injection during which the drug moves from the plasma to the rapidly equilibrating tissues. Often, there is a slower second distribution phase that is characterized by movement of the drug into the more slowly equilibrating tissues and return of the drug to the plasma from the most rapidly equilibrating tissues. The terminal phase is often called the "elimination phase" and the primary mechanism for decreasing drug concentration during this phase is drug elimination from the body by metabolism or excretion ***(Miller, 2000).***

So that, we can follow the processes that decrease propofol concentration over time following bolus injection. Initially, drug flows from the central compartment (plasma) to peripheral compartments through intercompartmental clearance and completely out of the body through metabolic clearance. Because there are three places for drug to go, the central compartment concentration decreases very rapidly, then the central compartment concentration falls to less than the concentration in the rapidly equilibrating compartment, and the direction of flow between them is reversed, so drug in the plasma only has two places to go: flow into the slowly equilibrating compartment and metabolic clearance. These processes are partly offset by the return of drug to the plasma from the rapidly equilibrating compartment. The

net effect is that once the rapidly equilibrating compartment has come to equilibration, the central compartment concentration falls far more slowly than before. Once the concentration in the central compartment falls to less than both the rapidly and slowly equilibrating compartments, then the only method of decreasing the plasma concentration is metabolic clearance. The return of drug from both peripheral compartments to the central compartment greatly slows the rate of decrease in plasma drug concentration ***(Miller, 2000)***

After a single bolus dose, two distribution phases are seen. The first phase has a half-life of 2 to 4 minutes. This is followed by a slow distribution phase with a half-life of 30 to 60 minutes. The termination of anesthetic effect after a single intravenous bolus or maintenance infusion is due to extensive redistribution from the brain to other tissues and to metabolic clearance. The terminal half-life ranges from 3 to 12 hours; with prolonged use, the terminal half-life may be longer. The pharmacokinetics of propofol don't appear to be altered by gender, chronic hepatic cirrhosis, or chronic renal impairment. Propofol crosses the placental barrier and is distributed into breast milk ***(Altmayer, 1994).***

Studies in which the pharmacokinetics of propofol was described by a three-compartment model have given initial and slow distribution half-lives of 1 to 8 minutes and

30 to 70 minutes and an elimination half-life of 4 to 23.5 hours ***(Altmayer, 1994).*** This longer elimination half-life is indicative of a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment. Owing to the rapid clearance of propofol from the central compartment, the slow return of propofol from this deep compartment contributes little to the initial rapid decrease in propofol concentrations. The context-sensitive half-time for propofol for infusions of up to 8 hours is less than 40 minutes ***(Hughes et al., 1992).***

Metabolism and clearance:

Hepatic metabolism and renal excretion:

Propofol is rapidly metabolized in the liver (10 times more than thiopentone) by conjugation to glucuronide and sulfate to produce water-soluble compounds, which are excreted by the kidneys. Less than 1 percent propofol is excreted unchanged in urine, and only 2 percent is excreted in feces ***(Takizawa et al., 2005).***

Propofol itself results in a concentration-dependent inhibition of cytochrome P-450 and thus may alter the metabolism of drugs dependent on this enzyme system ***(Chen et al., 1995).*** Propofol may impair its own clearance by decreasing hepatic blood flow ***(Leslie et al., 1995).***

The metabolites of propofol are thought not to be active. Because clearance of propofol exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination has been suggested. Extrahepatic metabolism has been confirmed during the anhepatic phase of liver transplantation ***(Hiraoka et al., 2005).***

The lungs do not seem to be the site of this extrahepatic metabolism; however, in vitro studies with human kidney and small intestine, microsomes demonstrated the ability of these tissues to form propofol glucuronide ***(Raoof et al., 1996).***

Distribution clearance:

Anesthetic drugs distribute extensively into peripheral tissues. This distribution into the periphery is represented pharmacokinetically as additional volumes of distribution that are attached to the central volume. Peripheral volumes are linked to the central compartment (plasma) by blood flow, a process called *"inter-compartmental clearance"* ***(Miller, 2000).***

Distribution clearance is the transfer of drug between the blood or plasma and the peripheral tissues. Unlike metabolic clearance, distribution clearance does not permanently remove drug from the body. Distribution clearance is a function of cardiac output, tissue blood flow, and the permeability of the capillary walls to the drug. For

a drug that is avidly taken up in peripheral tissues, such as propofol, the sum of the metabolic clearance and the distribution clearance approaches cardiac output. Tissue blood flow varies with cardiac output (COP), which, in turn, changes with disease and in response to many drugs. Concurrently administered drugs can also raise or lower cardiac output or alter the distribution of cardiac output (i.e., redirect regional blood flow). Virtually all anesthetics decrease cardiac output, and so anesthesia likely decreases intercompartmental clearance ***(Miller, 2000).***

Age, per se, only modestly reduces cardiac output in the absence of hypertension, coronary artery disease (CAD), valvular heart disease, or other cardiovascular disease. The net result is that advancing age modestly reduces intercompartmental clearance of anesthetic drugs ***(Miller, 2000).***

Clinical significance of pharmacokinetics of propofol:

Discontinuation of the recommended doses of diprivan injectable emulsion after the maintenance of anesthesia for approximately one hour, or for sedation in the ICU for one day, results in a prompt decrease in blood propofol concentrations and rapid awakening. Longer infusions (more than 10 days of ICU sedation) result in accumulation of significant tissue stores of propofol, such

that the reduction in circulating propofol is slowed and the time for awakening is increased. By daily titration of diprivan injectable emulsion dosage to achieve only the minimum effective therapeutic concentration, rapid awakening within 10 to 15 minutes can occur even after long-term administration. If higher than necessary infusion levels have been maintained for a long time, propofol redistribution from fat and muscle to the plasma can be significant and slow recovery occurs. The large contribution of distribution (about 50%) to the fall of propofol plasma levels following brief infusions means that after very long infusions a reduction in the infusion rate is appropriate by as much as half the initial infusion rate in order to maintain a constant plasma level. Therefore, failure to reduce the infusion rate in patients receiving diprivan injectable emulsion for extended periods may result in excessively high blood concentrations of the drug as shown in **Figure (2)**. Thus, titration to clinical response and daily evaluation of sedation levels are important during use of diprivan injectable emulsion infusion for ICU sedation ***(RxList, 2008).***

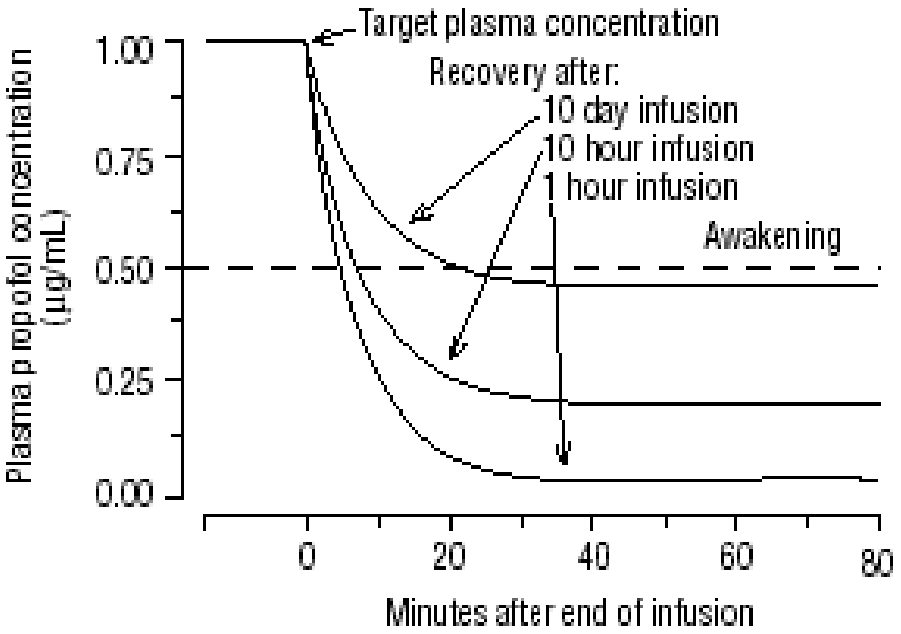

Fig. (2): Effect of duration of propofol infusion on its elimination ***(RxList, 2008)***

Because the required decrease in concentration for awakening following anesthesia or sedation with propofol is generally less than 50 percent, recovery from propofol remains rapid even following prolonged infusions ***(Hughes et al., 1992).***

Total body water is decreased in elderly persons and this smaller central volume of distribution leads to higher peak concentrations after a bolus or during the early part of an infusion. A decreased central volume of distribution partly accounts for the increased sensitivity of elderly patients to many anesthetic drugs ***(Miller, 2000).***