INTRODUCTION

Critically ill patients in an intensive care unit (ICU) are subjected to a variety of anoxious stimuli including pain after surgery, frequent venipuncture, invasive monitoring and endotracheal intubation so sedation is considered as an essential component of care in these patients ***(Hamimy et al., 2012)***.

Ideal sedative should be effective, short-acting and non-cumulative, free of adverse effects, having rapid onset and offset, with no effect on the metabolism of other drugs and lastly should have known pharmacokinetics and pharmacodynamics in organ failure ***(Hamimy et al., 2012)***.

Propofol (2,6-Diisopropylphenol) is very popular for sedating patients in the intensive care unit (ICU) because of its rapid onset and short recovery times, even after prolonged administration ***(Annecke et al., 2012).***

However, during the last 15 years there have been quite a lot of publications reporting unexplained deaths among pediatric and adult critically ill patients ***(Papaiaonnou et al., 2008).***

These cases shared common symptoms and signs unrelated with initial admission diagnosis and were under long-term propofol infusion at high doses. A new syndrome

called 'Propofol infusion syndrome' was defined ***(Papaiaonnou et al., 2008).***

PRIS was first described in children but it may also occur in adults, the pathophysiology is poorly understood ***(Annecke et al., 2012).***

PRIS is rare but usually leads to fatal cardiac and renal failure. Symptoms and signs are lactic acidosis, arrhythmia, hypotension, renal, cardiac and circulatory failure, oliguria, rhabdomyolysis, elevated serum creatine kinase, serum urea and serum potassium, lipemic plasma, liver enlargement, ketonuria, increased liver enzymes and green or red coloured urine. Risk factors identified from case reports are airway infection, severe head injury, increased catecholamine and glucocorticoid serum levels and low energy supply ***(Fudickar Bein, 2009).***

Occurrence is also associated with high propofol dosages (more than 4 mg/kg/hr), prolonged application (more than 48 hrs), and in patients with neurological or neurosurgical diseases. A case of fatal PRIS in a patient receiving the drug at a moderate dosage is also presented ***(Annecke al., 2012).***

AIM OF THE WORK

The aim of this essay is to review etiology, pathophysiology, clinical manifestations and complications of propofol infusion syndrome and main modalities for its management and prevention in critically ill patients.

PHARMACOLOGICAL BACKGROUND OF PROPOFOL

History

In 1973, in Cheshire, England, work on substituted phenol derivatives with hypnotic properties resulted in development of 2, 6 diisopropyphenol (coded as ICI 35868). The first clinical trial was conducted and reported by ***Kay &Rolly*** in Europe in 1977, using a 1% preparation formulated in Cremophor EL .There was high incidence of anaphylaxis with this formulation, so it was reformulated in lipid base emulsion, which became commercially available in the United Kingdom and New Ireland in 1986 and in USA in November 1989 **(*Simoni et al., 2013).***

Physicochemical Characteristics

Propofol is the approved name of 2, 6 di-isopropyphenol, its empirical formula is C_{12} $H_{18}O$; its molecular weight is 178.27 Dalton (fig. 1). It is a simple phenol substituted with 2 isopropyl groups in each of the position adjacent to the hydroxyl group.

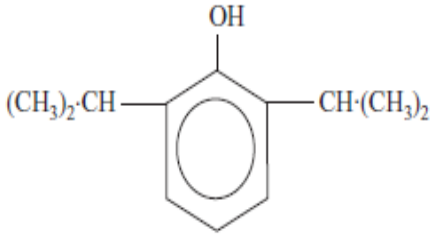

Figure (1): *Structure of Propofol* ***(Calvey &Williams, 2008)***.

It is pale straw colored oil and freezes at 19 °C. Its ionizable functional group, the hydroxyl, has a pka of 11, which renders it unsuitable to form salt in solution. The remaining parts of the molecule, the benzene ring and isopropyl groups are highly lipophilic. The result is a molecule that is almost insoluble in water but highly lipid soluble. So good propofol miscibility can be achieved in lipophilic substances and organic solvent ***(Silva et al., 2013).***

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).***

Different Propofol formulations

A-Cremophor EL Formulation

The first human trials of propofol were performed using a formulation of 2% propofol, 16% Cremophor EL and 8%

ethanol. 2% formulation as the potency of propofol was underestimated, Cremophor EL is a surfactant that facilitates dispersion of the drug molecule into the aqueous solutions, and 8% ethanol to eliminate the cloudiness. later 1% propofol, 16% Cremophor EL formulation was developed and used in Europe in 1977 ***(Simoni et al., 2013).***

The major side effect was histamine release, complement activation, severe hypersensivity and anaphylactic reactions. Pain upon injection was lessened after elimination of ethanol from formulation but still continued. It causes hyperlipidemia as it is degraded by serum esterase and release ricinoleic acid in blood stream. It can also cause peripheral neuropathy ***(Lim et al., 2010).***

B-Lipid based emulsions

The emulsion formulation having the same component as a parental fat formulation Intralipid®, i.e. 1% propofol, 10% soybean oil, 1.2% egg yolk lecithin and 2.25% glycerol. Soybean oil maintains the bulk of propofol in a medium that can be stabilized and dispersed, egg yolk lecithin works as an emulsifier to stabilize the propofol soybean oil droplets in aqueous dispersion, and glycerol maintains the emulsion isotonic with blood ***(Robertoet al., 2010).*** This 1% propofol formulation can support growth of some micro-organism such as Staphylococcus aureus, Escherichia coli, Pseudomonas

aeruginosa, and Candida albicans. So excipients were added to propofol emulsions, to inhibit bacterial growth upon extrinsic contamination ***(Baker & Naguib, 2005).***

C-Propofol EDTA (Diprivan®)

EDTA retards microbial growth at low concentrations, without affecting stability of propofol emulsion, pharmacokinetics or clinical profile. Aseptic precautions should be maintained during propofol administration. EDTA is an ion-chelating agent, it inhibit microbial growth by chelating vital trace metals. So infusion of propofol with EDTA was associated with mild decrease in ionized calcium and ionized magnesium throughout infusion. However, neither clinical manifestation, nor severe hypocalcemia (ionized calcium < 0.7mm) were reported. Ionized calcium concentration usually normalizes 30 min after discontinuation of infusion ***(Baker & Naguib, 2005).***

D-Propofol Sodium Metabisulfite

Sodium metabisulfite ($Na_2S_2O_5$) at a concentration of 0.25mg/ml acts by liberating small quantities of sulfur dioxide, that are capable of permeating microbes and being detrimental to the cell . The release of sulphur dioxide from aqueous phase increases as pH decreases. Therefore sulfite is more effective when pH is decreased, and sulfite containing propofol

emulsions have lower pH range (4.5-6.4) than those containing EDTA (7.0-8.5). The acidic media itself is in part responsible for inhibition of microbial growth, but cannot be used alone as it destabilizes emulsions ***(Baker &Naguib, 2005).***

In the presence of air it acts as a prooxidant reacting with oxygen, resulting in lipid peroxidation, as well as oxidation of propofol, which is responsible for emulsion discoloration. The consequences of these reactions and propofol products are not clear. Although sulfite is well known to cause allergic responses to certain individuals, no allergic responses to sulfite containing propofol have been reported ***(Simoni et al., 2013).***

E-Fospropofol

It is a phosphorylated prodrug of propofol which produces a unique pharmacokinetic and pharmacodynamic profile. Compared with propofol emulsion, it is associated with slightly longer time to peak effect and more prolonged pharmacodynamic effect ***(Gan, 2006).***

F-Ketofol

The combination of ketamine and propofol has received interest as a PSA regimen that allows the provision of PSA using drug doses lower than typically required for each agent alone, while the nauseant and psychic recovery effects of

ketamine are counterbalanced by the sedative and antiemetic effects of propofol ***(Arora, 2008).***

Pharmacokinetics

A-Absorption, distribution, metabolism, and excretion:

The high lipid solubility of propofol results into rapid onset of action, loss of consciousness occurs within 30 seconds. Awakening from single bolus injection is also rapid primarily due to rapid redistribution from highly perfused tissues (e.g. brain) to less well perfused tissues (e.g. muscles and fat), and to less extend metabolism and elimination ***(Hill, 2004).***

The pharmacokinetics of propofol is 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 ***(Rx List, 2008).***

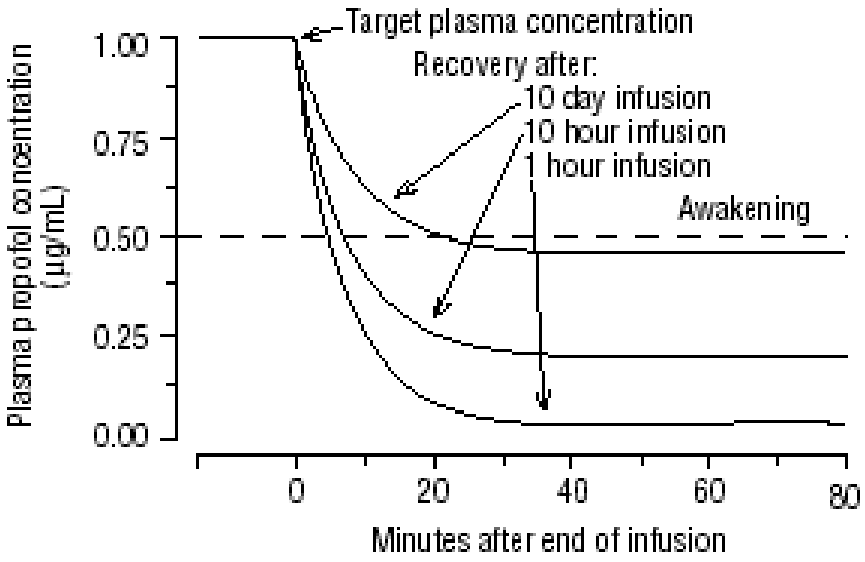

Figure (2): *Effect of duration of propofol infusion on its elimination* ***(RxList, 2008).***

Plasma concentration of propofol declines below the therapeutic level and awakening occurs (fig.2). As the drug concentration in central compartment becomes lower than in peripheral compartment, drug moves back to central compartment but in much slower rate, resulting into long elimination half-life. The complete elimination from body may take hours or days with little effect on recovery from its clinical effect as plasma concentration of propofol remains at sub therapeutic level. Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate to produce water-soluble compounds, which are excreted by the kidneys ***(Reves et al.,2010).*** Metabolites of propofol are water soluble and are primarily excreted in urine, Less than 1% propofol is excreted unchanged in urine, and only 2% is excreted in feaces. However

chronic renal failure does not affect clearance of the patent drug ***(Morgan et al., 2006).***

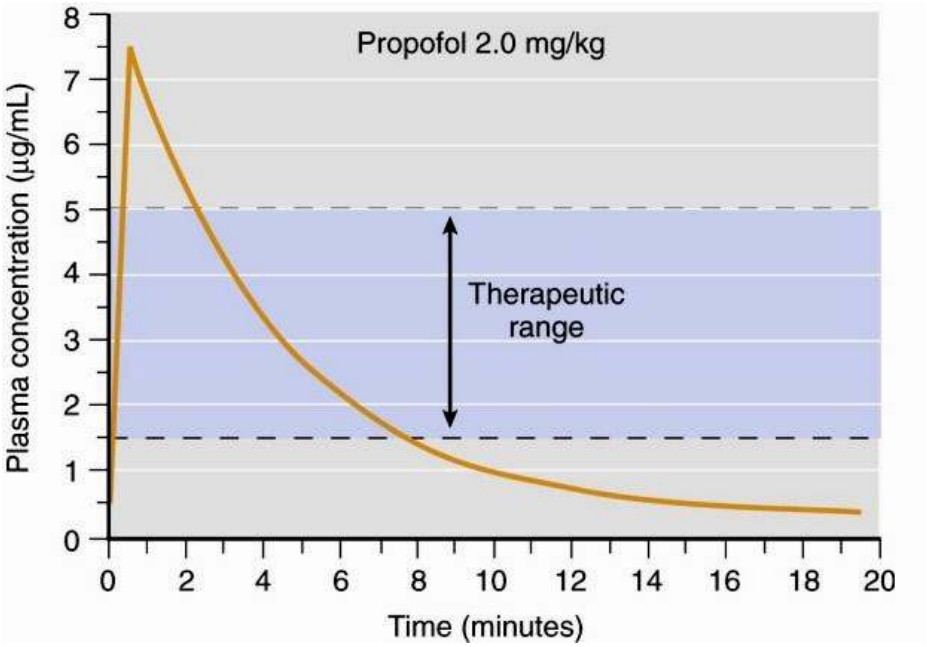

Figure (3): Simulated time course of whole blood levels of propofol after an induction dose of 2mg/kg. Blood levels required for anesthesia during surgery are 2 to 5 µg/ml, with awakening usually occurring at a blood level less than 1.5µg/ml ***(Reves et al.,2010).***

B-Factors affecting pharmacokinetics

Propofol's pharmacokinetics may be altered by:

Gender: women have larger volume of distribution (more subcutaneous tissues) and higher clearance rates but similar elimination half-life as males .This result into more rapid decline in propofol plasma concentration below therapeutic level, hence faster emergence in women after termination of infusion ***(Hoymork & Raeder, 2005).***

Age: children require higher induction and maintenance doses of propofol on a milligram per kilogram basis as a result of their larger central distribution volume and higher clearance rate. Elderly and poor health patients require lower induction and maintenance doses of propofol as a result of their smaller central distribution volume and decreased clearance rate with increased sensitivity of elderly patients to many anesthetic drugs ***(Laith, 2012).***

Propofol may decrease its own clearance by decreasing hepatic flow. It may also alter its intercompartmental clearance. An increase in cardiac output decreases propofol plasma concentration, and vice versa. So in hemorrhagic shock there is an increase in propofol plasma concentration of 20%, until uncompensated shock occurs, when rapid and marked increase in propofol concentration occurs, dose should be reduced ***(Wassim & James, 2009).***

Pharmacodynamics

A-Effects on central nervous system

Mode of action

Propofol induces hypnosis by selective modulation of $GABA_A$ receptor activity (fig.4). It enhances the current induced by gamma amino butyric GABA through binding to β subunits of $GABA_A$ receptor especially β_1 subunit (M286), β_2 subunit (M286), B_3 subunit (N265) of trans membrane domains.

These sites of action seem to be insensitive to GABA itself and they are quite distinct from the modulatory sites for barbiturates and benzodiazepines ***(Struys et al., 2005).***

None of effects of propofol are modified by the benzodiazepine antagonist. Propofol inhibits acetyl choline release in hypocampus through its action on $GABA_A$receptors. The α_2 adrenoreceptor system may play an indirect role in sedative effect of propofol ***(Kushikata et al., 2002).***

In addition, propofol results in a wide spread inhibition of N-methyl -D- aspartate (NMDA) subtype of glutamate receptor through modulation of sodium channel gating, this may contribute to its neuroprotective effects (fig.5). As stimulation of NMDA glutamate receptor lead to increase calcium and sodium influx to cells, resulting in activation of enzymes as proteases, lipases and endonucleases, causing cellular dysfunction and tissue injury ***(Kawaguchi et al, 2005).***

At sub hypnotic doses propofol provides sedation and amnesia. Awareness during surgery has been reported; extremely high infusion rates are required to prevent it especially if used as sole anesthetic. Propofol also tends to produce a general state of well-being, by increasing dopamine concentrations in nucleus accumbens. Hallucinations and sexual fantasies have also been reported with use of propofol ***(Pain et al., 2002).***

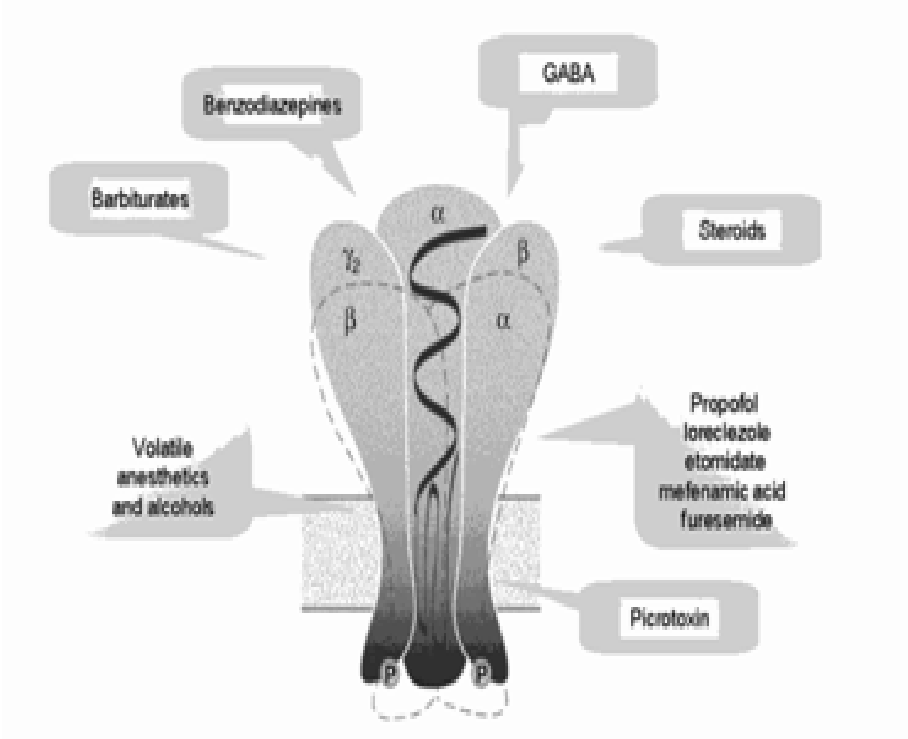

Figure (4): Schematic representation of the GABAA receptors illustrating its structure and the different sites of action for drugs that interact with this site the P designation represent the site of phosphorylation ***(Benke & Mohler, 2006).***

An induction dose of 1.5- 2.5 mg/kg produces rapid loss of consciousness and hypnosis, with peak effect seen at 90-100 seconds. In general closure of eyes is slower than with thiopental and the loss of verbal contact may be a more precise endpoint of loss of consciousness. The duration of hypnosis is dose dependent being 5-10 minutes after 2 to 2.5 mg/kg. Induction dose varies with age, being largest in children younger than 2 years and decreases with increasing age ***(Calvey &Williams, 2008).***

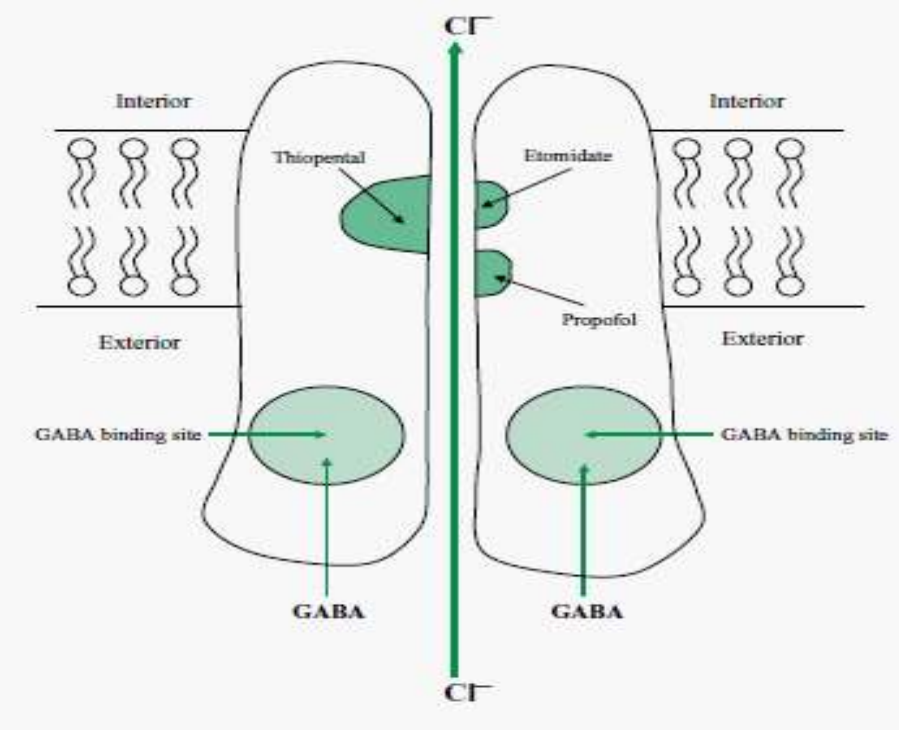

Figure (5): Site of action of different anesthetics on GABA receptor: The GABAA receptor contains an intrinsic ion channel that is selectively permeable to chloride ions., propofol and etomidate are believed to affect one or more modulatory sites that are distinct from the GABA binding site but closely related to the chloride channel,***(Calvey & Williams, 2008)***.

1. Anxiolytic effect

IV infusion of propofol at 0.2, 0.4, 0.5 or 0.7 mg/kg decreases anxiety score in patients undergoing urological surgery under regional anesthesia. The mechanism of anxiolysis involves a positive modulation of the inhibitory function of GABA through GABA receptors ***(Michael et al., 2013).***