DIISOPROPYL PHENOL (PROPOFOL) AS A NEW INTRAVENOUS ANAESTHETIC AGENT

Essay
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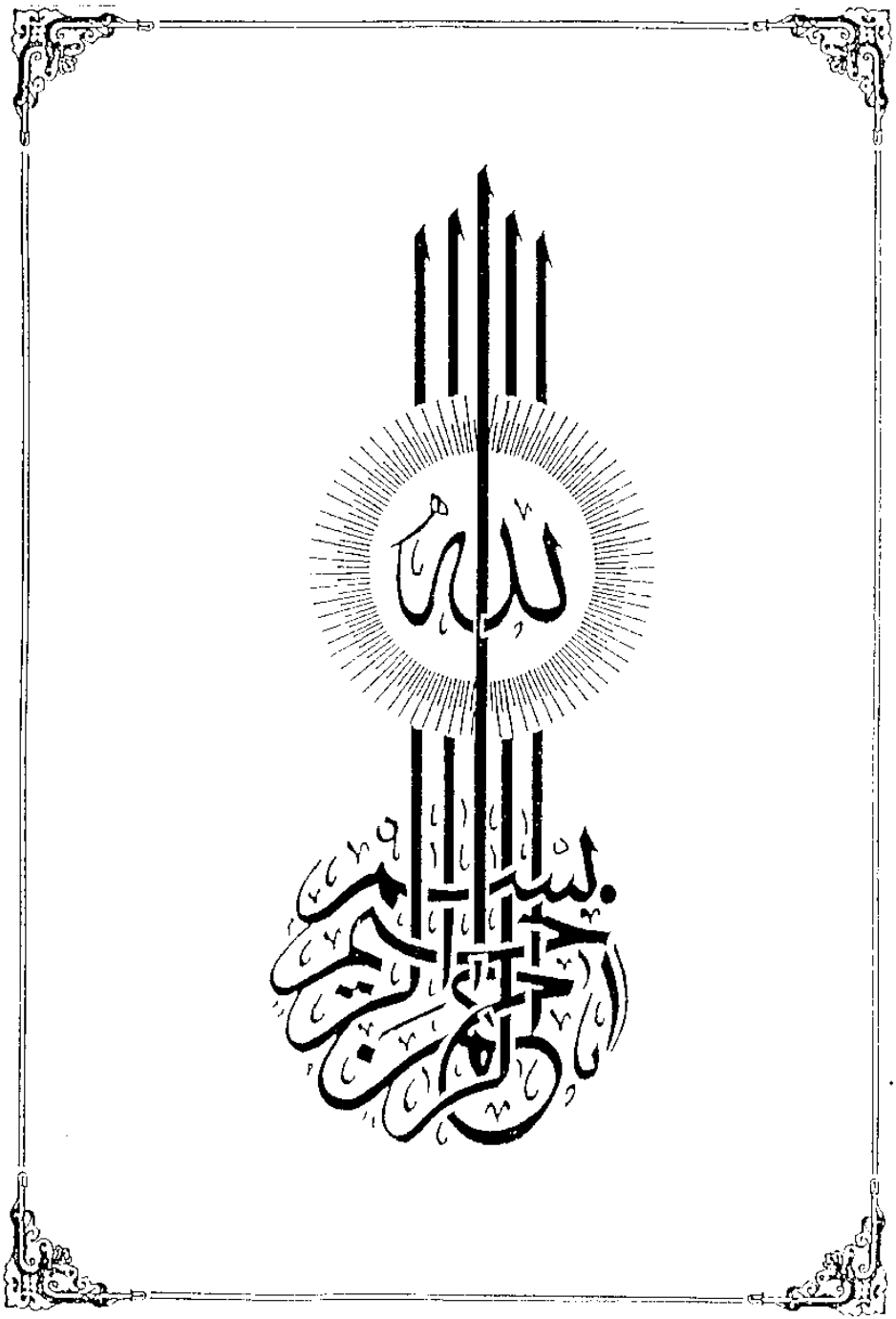
"بسم الله الرحمن الرحيم"

قالوا سبحانك لا علم لنا
إلا ما علمتنا إنك أنت العليم الحكيم"

"صدق الله العظيم"
سورة البقرة/ اية ٣٢



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INTRODUCTION

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The development of intravenous anaesthesia was hindered by the lack of suitable drugs, and it only really gained momentum with the discovery of the barbiturates. Initially several different barbiturates were developed for intravenous use. The first to make an impact was hexobarbitone in (1932), but it was soon displaced by thiopentone, which was probably first used by Waters in (1934). (*Dundee, 1984).*

No one will disagree that, from the patient's point of view, intravenous anaesthesia has been a major advance. the fear of suffocation from application of a face mask and the gradual loss of consciousness which some patients dislike are replaced by rapid and predictable loss of consciousness. Recovery is usually smooth, with less post operative sickness than some of the inhalational agents. The anaesthetist has the benefits of rapid induction with no 'second stage' of anaesthesia and its attendant delirium and the ability to follow (or precede) induction with a neuromuscular blocking drug of choice and easy tracheal intubation where appropriate. Uptack of subsequant inhalational agents is usually easy and one has the alternative choice of intravenous opioid supplementation

simplified by an 'open vein'. This may suggest that all that is needed is proficiency in venepuncture to employ intravenous anaesthesia. *(Dundee, 1985).*

Induction of anaesthesia by intravenous route has long been firmly established. The properties of the ideal intravenous agent have been discussed by *(Dundee, 1980).* It would like to have the physical properties of being, water soluble, stable in solution and on exposure to light over prolonged periods, not absorbed onto plastic or glass so that systemic availability is unaffected, non irritant on extravascular with no venous damage, no pain on injection, and have the pharmacological properties of being: produce sleep in one arm-to-brain circulation time, rapid metabolism so that there is no cumulation or hangover effect on recovery, no increasein muscle tone, myoclonia or respiratory upset on induction, minimum changes in the cardiovascular system, no effect on respiration, analgesia, although not essential, is desirable but antanalgesia should not occur, no interaction with neuromuscular blocking drugs compatible with other drugs used in anaesthesia, no effect on endocrine function, not associated with allergic reactions, no nausea or vomiting, no hepatotoxic effects in large doses and the metabolites should be non toxic.

the ideal intravenous anaesthetic does not excist. this is evidenced by the number of new such agents that appear from time to time. Unfortunately, many of these newer drugs, despite having several destinct advantages, suffered from disadvantages that were severe enough to warrant their withdrawal. *(Grounds et al., l985).*

2,6 diisopropyl phenol (Diprivan) has thus appeared at an important time in the development of intravenous anaesthesia. It was formulated previously in Cremophor El but is now prepared in an emulsion. Both preparations when given intravenously induce and maintain anaesthesia in humans, the dose requirements and anaesthetic properties are similar *(Glen and Hunter, l985).*

The formulation of propofol was changed because of the belief that cremophor El containing agents may be associated with a significant frequency of anaphylactoid reactions. The emulsion formulation of propofol would be less likely to produce anaphylactoid reactions. *(Blen and Hunter, l985).*

The clinical use of this new formulation was first reported by *(Nightingale et al., l984)* who confirmed the general efficacy

of propofol 2.5 mg/kg with subsequent rapid recovery without hang over effect.

Propofol in its emulsion formulation is a promising anaesthetic agents which was shown to posses many suitable characteristics of an ideal intravenous anaesthetic agent. these include the rapid smooth induction of anaesthesia, absence of excitatory effects, good maintenance of anaesthetic conditions followed by a rapid recovery, free from sickness *(N. Mackenzie and Grant, 1985).*

Propofol is a short acting intravenous anaesthetic which is suitable for both induction and maintenance of anaesthesia. Induction is rapid and smooth with low incidence of excitatory side effects. Most adult patients aged less than 55 years are likely to require 2-2.5 mg/kg of propofol for induction of anaesthesia. Over this age the requirement will be generally less *(Hilton et al., 1985).*

Anaesthesia can be maintained by administering propofol either by bolus injection when clinical signs of light anaesthesia appear or by continuous infusion with an average rate of 0.1-0.2 mg/kg/min. Recovery after anaesthesia is rapid and clear,

patients become well oriented within a short time after stopping the drug administration. *(Machenzie and Grant, 1985).*

Infusion of subanaesthetic doses of propofol have been used to sedate patients for surgery under regional anaesthesia. *(Fanard et al., 1988).*

Propofol is particularly suitable for out patient day case surgery with low incidence of nausea and vomiting after anaesthesia, patients very soon after surgery are able to drink or even eat before discharge. *(Sanderson and Blade, 1988).*

PHARMACOLOGY

- PHARMACOKINETICS

- PHARMACODYNAMIC

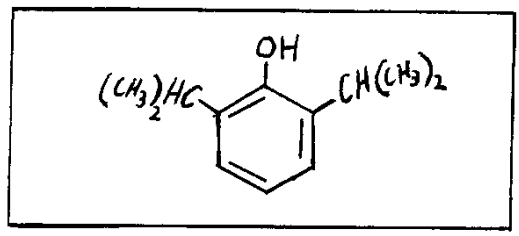
GENERAL AND CHEMICAL PROPERTIES

Propofol is the approved name of 2.6 disopropyl phenol.

The commercial name is Diprivan Imperial Chemical Industries (ICI)

Diprivan is a sterile oil-in-water emulsion formulated for intravenous injection and containing 1% Weight/Volume (w/v) of propofol.

The molecular weight of propofol is 178,



The structural formula of propofol

Propofol is one of a group of alkylphenols. At room temperature it is colourless to pale straw coloured liquid which is very slightly soluble in water (at 20°C). It has a Pka in water of 11.

The emulsion formulation of propofol contains propofol at a concentration 10 mg/ml and a soya bean oil 10% with egg phospholipid 0.5% as an emulsifier. Glycerol 2.25% was added to the solution to make it isotonic with blood. In this formulation it has a neutral pH 7.

Propofol is stable at room temperature and is not light sensetive.

If dilute solution of propofol is required it is compatible with 5 percent dextrose/water and should be prepared immediatly before administration and used within eight hours of preparation.

The precautions which applies to intravenous fat emulsion must be taken with propofol:

- it should be stored at room temperature i.e. below 25°C.
- it must not be frozen.
- each ampoule should be shaken before use.

- filters with pore size <l0 microns should not be used during administration of the emulsion.
- any proportion of the contents of an ampoule remaining after use should be discarded.
- the formulation should not be mixed with other therapeutic agents or infusion fluids prior to administration.