Propofol

Introduction
Propofol (2,6-Diisopropylphenol, C₁₂H₁₈O) is a derivative of alkyl phenol, which is used as an anesthetic in human and veterinary medicine.

Structure

CAS-number: 2078-54-8
molar mass (C₁₂H₁₈O) 178.27g/mol
density 0,96 g/ml
melting point 18°C
boiling point 256°C
pKa 11.1
water solubility 124mg/l (25°C)
LD50 500mg/kg (rat)
             386mg/kg (men, intravenous)

History [2]

The disinfectant effect of phenol was discovered in the 19th century, and the first reports on the antibacterial properties of propofol were published in 1954-1963. Up till then interest in propofol was focused on non-medical issues.

Propofol as anesthetic was first developed in the UK by ICI (Imperial Chemical Industries) in 1977 and launched under the name Diprivan (consisting of another mixture) in 1986 by Astra Zeneca (former ICI). Diprivan was licensed after clinical studies in 1988 in Germany and in the USA by the Food and Drug Administration in 1989.

Propofol, previously common only in medical institutions, became famous

Chemical and physicals properties[1]
Propofol is a clear, colorless to light yellow liquid.
in 2009 as the drug that caused Michael Jackson’s death.

**Synthesis**[^3]

Propofol can be synthesized in a number of ways. A synthesis, consisting of three steps and applicable in laboratories starts with phenol, which is alkylated by Friedel-Crafts alkylation. It is necessary to protect the most reactive para-position first. This can be done by sulfonation with concentrated sulfuric acid; as the sulfonyl substituent is a deactivating one, further sulfonation is not a problem. The free ortho positions can be alkylated with isopropyl alcohol in hydrochloric acid. Sulfonation is reversible and can be reversed after alkylation through heating in dilute sulfuric acid.

A more technical way of synthesizing propofol is to transfer phenol together with propene in an autoclave under pressures up to 3000 atm at 240-275°C. The reaction is catalyzed by Al(OPh)$_3$. (For reaction schemes see the attachment)

**Application and effect**[^4]

Propofol is used as a sedative in endoscopies and for patients in intensive care. As an anesthetic it induces and, if constantly administered, maintains a state of unconsciousness. Because Propofol is a hypnotic rather than an analgetic, it is administered in surgery along with analgetics (e.g. Fentanyl). It is administered intravenously as an emulsion with soya oil due to its poor solubility in water. The half-life period in the body ranges from one to three hours. Precise dosage is very important because of the low therapeutic index. Exceeding this index may cause several side effects, including respiratory disruptions, rapid blood-pressure decline and cardiac arrhythmia. If administered over longer periods, the so called Propofol-Infusion-Syndrome can occur. This is a disruption of metabolism and promotes cardio-vascular insufficiency. Pain can be reduced during injection by using a local anesthetic as additive (Lidocaine).

An option for prolonging the effect of propofol is to use the so called prodrug “fospropofol”. This is a phosphorylated variant of propofol that has higher solubility in water and does not generate its effect in the body until it is dephosphorylated by the enzyme “alkaline phosphatase”.

[^3]: http://www.thejerklnc.com/blog/?p=647
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Positive aspects of the use of propofol include comfortable awakening, and a reduced incidence of illness and vomiting after an operation. Another advantage is that the substance can be used for allergic patients, because histamines are normally not released.

The pharmacological effect of propofol consists in the interaction with the GABA<sub>A</sub> receptor in neurons. The GABA<sub>A</sub> receptor is part of chloride channels in neurons. γ-Amino-butryric acid is a neurotransmitter that opens the chloride channel by interacting with the GABA<sub>A</sub> receptor. Propofol binds with the beta-unit of the GABA<sub>A</sub> receptor and amplifies the effect of the neurotransmitter so that the conduction of nerve impulses is interrupted.

Loss of consciousness is caused by this interruption and leads to a breakdown of communication between cells in the central nervous system (CNS). Several studies indicate that propofol also disrupts the synaptic conduction of stimuli. The question of the exact action of the substance in the body has not been resolved but is still under investigation.

Propofol is mainly metabolized in the liver to glucurone derivatives. It is exuded by the kidneys; the metabolites can give urine a green to brown color.

Drug abuse<sup>[5]</sup>

Due to its pleasant side-effects, such as relaxation, propofol abuse is a serious issue. Abuse mainly occurs among medical personnel, as the substance is hardly available to other groups, although it is not subject to legal restrictions.

Abuse of propofol leads to psychological dependence (physiological withdrawal syndromes normally don’t occur) due to the manipulation of the mesolimbic-dopaminergic system (or reward system). Propofol abuse is hard to detect because of the short effect and half-life of the substance. Especially problematic is the low therapeutic index of the drug. Because consumers normally don’t remain under medical observation, those dependent on propofol cannot be medicated in the event of an overdose. This is the reason for the relatively high fatality rate associated with propofol abuse.
Conclusion

Propofol is one of the mostly frequently used anesthetics in medicine due to its advantageous properties. The negative aspects, including in particular the danger of drug abuse and dependence, are negligible, provided the substance is administered professionally and not over longer periods. The clarification of propofol’s mechanism of effect could lead to the development of new and better anesthetics.

Literature


http://en.wikipedia.org/wiki/Propofol

Revue d'histoire de la pharmacie, 84e année, N. 312, 1996. pp. 402-405

