

PROPOFOL, PAST, PRESENT AND FUTURE...

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The anaesthetic activity of ICI 35838 (2,6-diisopropylphenol) was first observed in mice on 23 May 1973. In 1986 this new short acting intravenous hypnotic was released for clinical use in adults for induction and short-term maintenance of anaesthesia as propofol in an emulsion formulation ('Diprivan'). As experience was gained, use extended to long-term maintenance, intensive care sedation, sedation as a supplement to loco-regional anaesthesia and use in children..

Propofol was discovered in the Biology Department at ICI Pharmaceuticals Division. Over a ten year period more than 5000 compounds were tested as potential new anaesthetics. Anaesthetic activity was discovered in a series of alkylphenols and among these, ICI 35868 was selected as a candidate drug [1, 2]. A desirable pharmacological profile was observed at an early stage but many of the 13 years of pre-clinical development were required to find an acceptable alternative to Cremophor, the solubilising agent which had been used in 'Althesin' (alphaxalone/alphadolone) and 'Eponol' (propanidid). A model was developed in pigs, which demonstrated that Cremophor EL was likely to be responsible for many of the anaphylactoid reactions that had been encountered with these preparations [3]. Further research led to the development of the current soybean oil emulsion formulation of propofol.

In 1977 Dr Brian Kay working with Prof Rolly in Belgium conducted the first clinical trial in patients with a formulation containing 2% propofol in 16% Cremophor and 8% alcohol. This study confirmed anaesthetic properties in man with 0.94 mg/kg being the mean effective dose in unpremedicated patients, but a high frequency of pain on injection was reported [4]. This led to the removal of alcohol from the formulation and the propofol concentration was reduced to 1%. As clinical work in other centres progressed, it became apparent that the generally effective induction dose was in the region of 2.0 mg/kg.

While the search for a non-Cremophor formulation went on, clinical studies continued with the Cremophor formulation in patients who had not been previously exposed to this material. By 1981, about 1000 patients had been studied with propofol in the Cremophor formulation but a number of anaphylactoid reactions had been observed and it was decided that no further studies would be done with this formulation. Two years of detailed pharmaceutical work were required to achieve a stable emulsion formulation and pharmacology studies confirmed that a desirable anaesthetic profile was maintained [5]. In July 1983 clinical studies were restarted with this formulation to confirm and extend the information gained with the earlier formulation and a Product Licence Application was submitted in Feb 1985.

The initial use of propofol was for induction of anaesthesia and short-term maintenance, mainly by incremental injection. However it was clear that propofol had a suitable pharmacokinetic profile to allow its use by continuous infusion to maintain anaesthesia or to provide sedation for patients receiving intensive care. Other agents suitable for use by infusion had either been withdrawn ('Althesin' and 'Eponol') or as in the case of etomidate, concern had been expressed at the effect of an infusion on adrenocortical function.

Early studies evaluating the use of propofol by infusion for maintenance utilised a range of dosing schemes aimed at the achievement of a steady blood propofol concentration. Among these the Bristol '10-8-6 mg/kg/h' scheme was one of the most popular [6]. One barrier to the wider use of infusion techniques was the 99 ml/h maximum rate of infusion of most syringe pumps available at this time. The development of the Ohmeda 9000 pump was a major step

forward with infusion rates up to 1200ml/h making induction of anaesthesia by infusion a practical proposition [7]. The development and validation of equipment for the administration of propofol by target controlled infusion (TCI) was an important step in facilitating wider use for maintenance of anaesthesia.

Along the way, the acceptance of propofol was facilitated by the concurrent introduction of the laryngeal mask and the growth in day case procedures. Issues that had to be dealt with included misuse in the US leading to extrinsic bacterial contamination and the incorporation of an antibacterial additive in the emulsion. Reports of a possible 'propofol infusion syndrome' have led to a restriction of use for sedation in children and a need to avoid excessive dosage when propofol is used for prolonged sedation in adults.

Some topics generating discussion at present include open TCI systems and the confusion being caused by different implementations and different pharmacokinetic models for propofol, new systems for patient controlled sedation, propofol monitoring in expired air and a high profile case of propofol abuse.

In the future it is possible that current research with propofol in closed loop control systems may lead to wider use of this approach. Potential competitors under development may replace some of the current use of propofol. Interesting compounds are the esterase-metabolised agents THRX- 918661, CNS 7056 and MOC-etomidate. Anaesthetists have led the way in the clinical application of TCI and it is possible that this approach could be applied with benefit in other therapeutic areas. Finally some of the observations made in the development of propofol suggest some avenues for basic research on pain mechanisms and immunology.

References:

- [1] Glen JB. Br J Anaesth.1980; 52: 731-42.
- [2] James R Glen JB. J Med Chem. 1980;23:1350-57.
- [3] Glen JB, et al. Br J Anaesth.1979;52: 819-27.
- [4] Kay B, Rolly G. Acta anaesth.belg. 1977;28: 303-16.
- [5] Glen JB, Hunter SC. Br J Anaesth. 1984; 56: 617-25.
- [6] Roberts FL et al. Anaesthesia 1988; 43 Supp: 14-17.
- [7] Stokes DN et al. Anaesthesia 1990; 45: 1062-66.