

# Propofol has withstood the test of 20 years at the forefront of anaesthesia

In the seventh article in a series on landmark drugs, Jenny Bryan looks at propofol, an intravenous anaesthetic that remains in mainstream use

When the intravenous anaesthetic propofol (Diprivan) was launched in the UK in 1986, it could not have arrived at a better time. For two years anaesthetists had been relying mainly on the barbiturates thiopentone and methohexitone to put patients to sleep, following the withdrawal of the widely used steroid agent Althesin in 1984 owing to severe allergic reactions to its solvent. The barbiturates had the drawback that people were drowsy for long periods after they woke up from surgery, so the short-acting propofol was a welcome arrival.

“The loss of Althesin was very significant because it was very useful for minor procedures, and there was less accumulation than with the barbiturates, so it could be given in multiple injections. When propofol came along, it filled the hiatus which had been left by Althesin’s withdrawal,” recalls David Greaves, consultant anaesthetist at the Royal Victoria Infirmary, Newcastle-upon-Tyne.

Propofol (2,6-diisopropylphenol) was discovered in the early 1970s at the research laboratories of ICI, and early dose ranging studies suggested that it compared well with Althesin.<sup>1,2</sup> While its lipophilicity ensured that propofol could cross the blood brain barrier, its lack of water solubility resulted in formulation difficulties.

Initially formulated in the same cremophor EL solvent that proved the undoing of Althesin, propofol was subsequently reformulated in a soya bean emulsion that produced significantly smoother induction of anaesthesia than thiopentone and methohexitone, and superior post-anaesthetic recovery.<sup>3</sup> Today’s formulation of propofol has an additional lipid component, though a variety of experimental formulations have been tested, including a water-soluble prodrug formulation,<sup>4</sup> and a sublingual product. However, none of these has overcome the fundamental problem that propofol injections hurt.

## Mechanism of action

The precise mechanism of action of propofol remains unclear, as with many anaesthetics. Most of its pharmacological actions are thought to result from interaction with the GABA(A) receptor to enhance inhibitory synaptic transmission, or with calcium channels,<sup>5</sup> although it has been suggested that activity at 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptors may account for the low rates of postoperative nausea and vomiting associated with propofol.<sup>6</sup>

When it first came out, the main drawback of propofol was cost. Dr Greaves remembers



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it as one of the first drugs to be introduced that was so expensive that hospitals put restrictions on its use, initially banning it altogether, and then limiting it to use by consultants. However, growing pressure on surgeons to carry out more procedures as day cases proved the saviour of propofol, whose lack of hangover effects and low rates of post-operative nausea and vomiting made it much more suitable for day surgery than the cheaper barbiturates.

“Propofol knocked methohexatone off the market because it was better for short cases and emergencies and, not least, because it was new,” says Dr Greaves.

The introduction of the potent, short-acting opioid analgesic alfentanil at around the same time as propofol produced a promising combination and, when Alfentanil was replaced by the easier to use remifentanil, anaesthetists had what became the gold standard for total intravenous anaesthesia.

But lingering concerns about the risk of drug accumulation when anaesthesia is maintained intravenously have meant that, in most cases, propofol continues to be used for induction of anaesthesia, with patients then transferred to inhaled agents.

“Since the 1950s, anaesthetists have been putting patients to sleep with a barbiturate or,

more recently, with propofol and then taking over the sleep component of anaesthesia with an inhaled agent, such as isoflurane, and using separate intravenous agents for muscle relaxation and analgesia,” explains Dr Greaves. “In contrast, the total intravenous technique involves keeping the patient asleep with propofol, using remifentanil as an analgesic and ventilating with a mixture of air and oxygen.”

In 1996, AstraZeneca introduced a target controlled infusion (TCI) system, called Diprifusor, in an effort to simplify the administration of propofol, so that anaesthetists would feel as comfortable about altering the depth of anaesthesia with the IV product as with inhaled anaesthetics.<sup>7</sup> The anaesthetist enters the body weight and age of the patient and the target blood concentration of propofol for a particular effect, and the Diprifusor microprocessor controls the rate of infusion. The depth of anaesthesia can then be adjusted by changing the requested target concentration.

“The machine makes a ‘best guess’ and it can be relatively inaccurate because it’s easy to adjust the target concentration according to whether you want the patient to be more lightly or deeply anaesthetised, and you can monitor the EEG throughout the procedure as an early warning of any problems,” Dr Greaves explains.

Propofol's rapid onset and short duration of action — and the ease with which it can now be given — has not just made it a favourite with anaesthetists: it has become a popular alternative to intravenous benzodiazepines for sedation during endoscopic procedures and, in some centres around the world, propofol is administered without an anaesthetist being present.

The Royal College of Anaesthetists warns against this practice, and Dr Greaves stresses that anaesthetics should only be administered by people who are trained and experienced in dealing with unexpected consequences.

“Physicians and sedation nurses are trained to deal with patients who suddenly collapse but, as problems are so infrequent, they don't stay expert in emergency procedures. If a patient stops breathing you need to act very quickly to prevent them dying or being severely brain damaged,” he points out.

In addition to its use for anaesthesia induction and maintenance, propofol is also widely used in intensive care units (ICUs) to sedate patients who are being ventilated. The emergence of so-called propofol infusion syndrome (PIS) — a rare but potentially fatal syndrome described mainly in critically ill children undergoing long-term high-dose propofol sedation, but also in some adults — has meant that patients do not usually remain on propofol for more than three days at a time. The main features of the syndrome are

cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure.<sup>8</sup>

A review of cases carried out by AstraZeneca, showed that the main risk factors for PIS are poor oxygen delivery, sepsis, serious cerebral injury and high propofol dosage.<sup>9</sup> Increasing lipaemia, thought to be due to a failure of hepatic lipid regulation, possibly related to poor oxygenation or lack of glucose, or both, was found to be an early warning of PIS in some cases, leading to sequestration of propofol into the lipid phase, lowered free propofol levels and apparent insensitivity to the drug. AstraZeneca, therefore, recommended good haemodynamic and oxygen delivery management, with adequate glucose provision, adherence to propofol dosing regimens and active management of lipaemias.<sup>9</sup>

### Still in mainstream use

Despite the failure wholeheartedly to embrace its use for total IV anaesthesia and the limitations on ICU administration, propofol has more than withstood the tests of two decades at the forefront of anaesthesia. As Dr Greaves concludes: “It doesn't have a legacy because propofol is still in mainstream use. It has certainly changed practice because it has opened up opportunities for total IV anaesthesia for those who are interested in that approach. But it's disappointing that the relatively low value of the anaesthetic market

has meant that pharmaceutical companies have taken so little interest in developing new anaesthetic agents since propofol.”

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