VIEWPOINT

The Discovery and Development of Propofol Anesthesia
The 2018 Lasker-DeBakey Clinical Medical Research Award

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The 2018 Lasker-DeBakey Clinical Medical Research Award has been presented to John B. (Iain) Glen for the discovery and development of propofol, a chemical whose rapid action and freedom from residual side effects have made it the most widely used agent for induction of anesthesia in patients throughout the world.

The specialty of anesthesiology commonly traces its origin to a demonstration by William Morton of the inhalation of ether by a patient undergoing surgery in Boston in 1846. This followed the earlier observation of the analgesic property of nitrous oxide by Davy in 1840 and the use of this agent for painless dentistry by Wells in 1844. Ether was the more potent agent and thereafter painless surgery soon became the norm in many countries. To this day, modern inhalational anesthetic agents are still widely used to maintain unconsciousness, but they are now generally preceded by the administration of an intravenous anesthetic to achieve unconsciousness more rapidly than can be achieved with an inhalational agent administered through a face mask. Since its introduction in 1934 by Lundy, thiopentone, because of its ability to provide rapid loss of consciousness without accompanying excitatory adverse effects, had become the intravenous induction agent of choice.

Advances in Anesthesia Research

Imperial Chemical Industries (ICI) Pharmaceuticals Division (which demerged from the parent company to become Zeneca, and subsequently merged with Astra to form AstraZeneca) had achieved success in anesthesia research with the discovery by Raventos in 1956 of the inhalational agent halothane, a rapidly acting, nonflammable agent that largely replaced the use of ether. In 1972, Iain Glen, a veterinarian with a special interest in veterinary clinical anesthesia and research at Glasgow University in Scotland joined the anesthetic project team at ICI, which had recently embarked on the search for a new intravenous anesthetic agent. With his knowledge of the profile of established intravenous anesthetics in animals, Glen's role was to head the biology group responsible for the evaluation of potential new agents submitted by project chemists, with a cascade of tests to detect compounds with desirable properties.

The new agent sought was one that would reproduce the desirable properties of thiopentone as an induction agent, but would differ because it would be more rapidly metabolized, such that it could be given by repeated injection or by infusion to maintain anesthesia without the delay in recovery that would occur were thiopentone to be used in this manner. There are situations in which inhalation anesthesia is inappropriate, such as for patients who are susceptible to malignant hyperthermia, and at this time, before effective systems to scavenge waste anesthetic gases had been installed, there was concern about the possibility of harm to operating room staff from prolonged exposure to these agents.

To gain access to the brain, any molecule with anesthetic activity needs to be relatively lipophilic, but to facilitate intravenous injection and compatibility with blood an aqueous solution is required. One method to achieve this, as was the case with thiopentone, is to prepare a water-soluble salt of a weak acid or base that is able to dissociate back to the free acid or base in blood. The chemical team had initially focused on many structurally diverse weak organic bases, anticipated to be relatively lipophilic in their unionized forms, but no candidate drug had emerged. Around this time a eugenol derivative, propanidid (Epontal [Bayer]), and the steroid combination of alphaxalone and alphadolone (Althesin [Glaxo]) had been introduced as short-acting intravenous anesthetics. Both of these lipophilic agents were presented as aqueous dispersions with the aid of a polyethoxylated castor oil surfactant (Cremophor EL [Bayer]). The availability of this surfactant now allowed poorly water-soluble compounds, previously synthesized by ICI chemists, to be tested in animals for anesthetic activity.

Discovery and Development of Propofol

In May 1973, hypnotic activity was detected in 2,6-diethylphenol, one of a selection of poorly water-soluble agents selected by James, a project chemist from ICI's compound collection. Because its onset of effect was slow this compound was discarded, but it provided a lead for the systematic evaluation of related alkyl-substituted phenols.[1] Among these Glen selected propofol (2,6-diisopropylphenol[ICI 35 868], previously synthesized as a potential antibacterial agent) as the only compound with the optimum balance of properties and acceptable effects on respiration and circulation. In comparison with thiopentone, propofol could be given by repeated injection without prolonging recovery and was free of the "'hangover" effects that thiopentone produced. Mice given propofol were able to balance on a horizontal rod only 3 minutes after regaining consciousness, whereas mice given thiopentone needed more than 40 minutes to reach the same end point.[2]

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Because pure propofol is an oil, the search for an acceptable formulation led to a 13-year delay before the new agent could be marketed. Occasional anaphylactoid reactions were reported in patients given the 2 anesthetics formulated with Cremophor, and it was unclear if these were attributable to the active agents or the surfactant vehicle. This led Glen and colleagues to conduct a systematic evaluation of Cremophor-containing agents in pigs. It was found that, after an uneventful first exposure, a second injection given 1 week later produced a marked anaphylactoid response, a typical feature of which was a marked but transient reduction in blood polymorph count suggestive of complement activation.[3] Clinical trials had begun with a Cremophor formulation of propofol but, working with Priaulx in ICI's pharmaceutical department, Glen identified a totally synthetic surfactant (Synperonic) that was well tolerated in his pig model. Pharmacology and toxicology studies were repeated over the next 2 years but histological changes in liver halted work with this formulation.

Clinical trials had continued with the Cremophor formulation but in 1980, when more than 1000 patients had been studied, a number of anaphylactoid reactions were encountered and clinical trials were halted. Earlier attempts to produce an emulsion formulation had failed, but as emulsion manufacturing technology improved, it was agreed in 1981 that the biology team, working with Kent in the pharmaceutical department, could reopen work on the development of an emulsion formulation. These studies confirmed that a formulation containing soybean oil and purified egg lecithin retained the desirable properties of propofol and was well tolerated in the pig model.[4]

Clinical trials with the emulsion formulation of propofol began in 1983, and Glen joined the team led by Stark to assist with international trials and clinical pharmacology studies. It was reassuring to find that the clinical trials confirmed the benefits that had been predicted from animal studies. The first approvals for use of propofol in induction of anesthesia and short-term maintenance of anesthesia were obtained in 1986. The clinical trial program in the United States had begun later, and approval by the US Food and Drug Administration (FDA) followed in 1989. Subsequent approvals for long-term maintenance of anesthesia, intensive care sedation, use in children, and sedation for investigative procedures or for surgery conducted with regional anesthetic techniques followed.

The limited infusion rate range of syringe pumps was recognized as a barrier to the wider adoption of continuous infusion techniques, and Glen encouraged the development of the Ohmeda 9000 device as the first of a new generation of pumps suitable for both induction and maintenance of anesthesia or sedation.[5] The technique of target-controlled infusion (TCI), wherein a pharmacokinetic model for the drug to be infused[6] is incorporated in the pump software and a program calculates the infusion rate required to achieve a desired drug concentration, was introduced by Schwilden in 1981. Beginning in 1990, meetings were hosted with international groups with a research interest in this area, and in 1992 ICI agreed to develop a Diprifusor TCI module that could be incorporated in a compatible syringe pump to allow infusion of propofol to achieve a target blood concentration and to facilitate regulation of depth of anesthesia.[7] This module incorporated software developed by Kenny and White in Glasgow and was constructed and validated by Gray. Further clinical trials and a complex regulatory program led to the introduction of this technique in most countries beginning in 1996, but not to date in the United States where it remains unapproved by the FDA.

The benefits of propofol including rapid, clear-headed recovery and a reduced likelihood of postoperative nausea and vomiting, together with its compatibility with the laryngeal mask airway, rapidly became appreciated worldwide such that propofol has now to a large extent replaced the use of thiopentone. Its use has facilitated the wider adoption of ambulatory surgery with early discharge welcomed by patients. In the United Kingdom alone, a recent survey indicated that propofol was used in more than 2 million procedures in 1 year.[8]

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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