ELSEVIER

Propofol as a transformative drug in anesthesia: insights from key early investigators

Brian T. Bateman and Aaron S. Kesselheim

Brigham and Women's Hospital, 1620 Tremont St, Suite 3030, Boston, MA 02130, USA

To study the process of drug development in anesthesiology, we identified what expert anesthesiologists considered the most transformative new product in the field over the past 25 years – propofol (Diprivan®) – and conducted an in-depth qualitative study into the features of its development. Experts with insights into propofol development were subjected to semi-structured interviews about their experiences with the drug. We found a number of important themes helped contribute to its discovery, such as positive aspects of the environment at Imperial Chemical Industries (ICI). Individual anesthesiologists outside the company took a central role in driving the development process forward and ultimately making the product transformative. This episode provides lessons for drug developers interested in promoting similar transformative drug innovation.

Background

During recent years, there have been widespread reports of a global crisis in new drug development [1,2]. Whereas the extent of the crisis has been widely debated [3], data show that spending on drug R&D by the public and private sectors has risen [4,5] without proportionate increases in the number of new drugs being approved. As various commentators have noted, there has even been a decline in new transformative drugs that lead to major advances in patient care [6,7].

Transformative drug development has been particularly limited among anesthetic agents [8]. Recently approved agents such as fospropofol (Lusedra®) and sugammadex (Bridion® in the EU) only offer modest clinical advances. Other promising new drugs under active development in this field are structural analogs of known compounds with similar mechanisms of action [9–11]. Lack of originality in drug development in the field led one expert to wonder why anesthesiologists have moved away from the model of innovative 'clinical pharmacologists' [12]. Two pharmaceutical-industry-based scientists reviewing the state of R&D concluded 'there is little need for new drugs in anesthesia because the needs of anesthesiologists are well covered with existing agents' [13].

Understanding the development of agents that have gone on to be transformative from the perspective of those closely involved in the process could provide insights that inform future drug development efforts in the field of anesthesia. It is also important in documenting recent history that is foundational to the modern practice of anesthesia. We therefore queried thought leaders in anesthesia to identify the most groundbreaking new anesthetic product approved in the past 25 years. We then conducted interviews of several key participants in its discovery and development.

Identification of the most transformative drug in anesthesiology

In 2010–2011, one of us (A.S.K.) conducted a modified Delphi protocol survey to identify the most transformative drug approved by the FDA in each medical field, including anesthesiology [14]. Participants came from the top 30 academic medical centers in the USA receiving the greatest amount of biomedical research funding from the National Institutes of Health (NIH) in 2009, as well as their primary affiliated hospitals (two institutions had two different hospitals). Each clinical chief of anesthesiology was sent an email invitation to participate or nominate another expert member of the department (a US$100 honorarium was offered). We anticipated that physicians in such roles would have expertise in clinical practice and medical research, as well as sufficient experience to provide historical perspectives on how their fields have evolved. The 15 participants received an initial list of new molecular entities relating to anesthesiology approved between 1985 and 2009 and instructions to identify the five most-transformative products (for purposes of the study, 'most transformative' was defined as a drug that is innovative and has had a groundbreaking effect on patient care and healthcare delivery). All 15 participants (100%) selected propofol, whereas the next-most-common

Corresponding author: Bateman, B.T. (bbateman@partners.org)

http://dx.doi.org/10.1016/j.drudis.2015.04.007

Please cite this article in press as: Bateman, B.T., Kesselheim, A.S. Propofol as a transformative drug in anesthesia: insights from key early investigators, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.04.007

selections were remifentanil (11, 73%) and either sevoflurane or desflurane (12, 80%). Next, 80% of the participants reached consensus on propofol as the top most-transformative product from this group.

Interviewing key investigators

Based on personal contacts, publicly available regulatory documents and searches of the medical literature for seminal articles describing the discovery and preclinical and/or early clinical testing of propofol [15–18], we identified senior contributors or experts likely to have insights into the development of propofol. Of the 16 individuals on our initial list, two did not have contact information that was readily obtainable. Among the remaining 14 individuals, ten (71%) agreed to participate and four (29%) did not respond to our initial contact or a subsequent request to participate. Early interviewees provided an additional contact for our list, for a total of 11 participants (Table 1).

The investigators conducted telephone interviews with participants between November 2011 and March 2012. The interviews were recorded and transcribed. The median interview time was 42 min (range 20–69 min). The interview began by asking about where the idea for propofol originated, and participants were asked to detail their experiences in its discovery and/or development, as well as to comment on the rationales for the decisions that were made at each key step. We then probed interviewees further about the basis for the transformative utility of the drug in patient care, the institutions and individuals involved at each step in the development, the effect of the evolving practice of anesthesia and government regulators, the impact of intellectual property issues and the role of collaboration and/or competition among institutions and individuals.

Based on the interviews, we constructed a timeline of important events in the development of propofol. Then, with the aid of the NVivo 8 software package (QSR International, Melbourne, Australia) [19], we reviewed the transcripts of each of the interviews and coded each of the transcripts into dimensions reflecting the sections of the semi-structured interview (seven nodes, 43 secondary nodes) (Table S1 in Supplementary Material available online). We then assessed each node and secondary node separately to determine the key messages and points of commonality among the interviewees within each of the areas of interest. The study was approved by the Institutional Review Board at Brigham and Women's Hospital, and the need for written informed consent was waived.

Propofol development timeline

The discovery and preclinical testing of propofol (Table 2) occurred within the pharmaceutical division of a large British chemical company: Imperial Chemical Industries (ICI). In the late 1960s, a new lipid-soluble intravenous anesthetic, propanidid (Epontol®) was brought to market in Europe. Another, alfaxalone/alfadolone acetate (Althesin), followed in the early 1970s. These agents were dissolved in a newly available solvent named Cremophor® EL. Around the same time, ICI's pharmaceutical division had initiated a program to look for new volatile and injectable anesthetic agents. The availability of Cremophor® prompted scientists at ICI to initiate, in the early 1970s, the screening of libraries of lipophilic agents for anesthetic activity in mice. The first compound that drew attention was 2,6-diethylphenol, which had mild anesthetic properties. Building on this modest success, the ICI team, led by Dr Iain Glen, screened related alkylphenols for anesthetic activity and found that 2,6-diisopropylphenol (ICI35868) appeared to be a highly potent, short-acting anesthetic agent [20,21]. This later became the active ingredient in propofol.

Following about four years of preclinical studies in animal models, clinical testing of ICI35868 in Cremophor® started. The first administration in human patients was performed by Drs Brian Kay and Georges Rolly in Ghent, Belgium, in 1976 [15]. The investigators found that the agent was very rapid in onset and offset, and patients woke up feeling clearheaded and without the nausea typically associated with other anesthetic

TABLE 1

Study interviewees and their roles in propofol discovery and development.

Name[a] (alphabetical order)	Affiliation at time of contribution to propofol development	Brief description of role
David P. Coates	Bristol Royal Infirmary	Investigator in early clinical trials
Robert J. Fragen	Northwestern University	Investigator in early clinical trials
Iain Glen	Imperial Chemical Industries[b]	Led development efforts at Imperial Chemical Industries[b]
Carl C. Hug, Jr	Emory University Hospital	Investigator in Phase IV clinical trials
Brian Kay	Derby Children's Hospital/Ghent University	Performed first trial in patients
Cedric Prys-Roberts	Bristol Royal Infirmary	Investigator in early clinical trials, introduced use of propofol as continuous infusion
Carl E. Rosow	Massachusetts General Hospital	Nonaffiliated leader in the field
John W. Sear	University of Oxford	Investigator in early clinical trials
J. Robert Sneyd	Imperial Chemical Industries[b]	Led clinical trials that led to regulatory approval in Japan
Ron D. Stark	Imperial Chemical Industries[b]	Organized and led European clinical research team (1982–1986)
Paul F. White	Stanford University	Investigator in early clinical trials, demonstrated role for propofol as maintenance of anesthesia and its utility in outpatient surgery in USA

[a] The identification of an interview source on this list does not imply endorsement of the article or its findings.
[b] Imperial Chemical Industries Pharmaceuticals Division split from the parent company in 1992 and became Zeneca which later merged with Astra to form AstraZeneca.

Please cite this article in press as: Bateman, B.T., Kesselheim, A.S. Propofol as a transformative drug in anesthesia: insights from key early investigators, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.04.007