Editorial

Korean J Anesthesiol 2011 March 60(3): 149-150
DOI: 10.4097/kjae.2011.60.3.149

Increasing interest in PK and PD studies has many advantages for anesthesiologists

Young-Cheol Woo

Department of Anesthesiology and Pain Medicine, Chung-Ang University Hospital, Seoul, Korea

In this issue of the Korean journal of anesthesiology, Bae and colleagues [1] studied the induction and maintenance dose of propofol for anesthesia in major burn patients. They reported that an induction dose of 1.5 mg/kg is appropriate and a slow infusion rate of 20 mg/kg/hr is safe for maintaining the desirable hypnotic condition and this causes no significant hemodynamic problems. Many pathophysiologic alterations in patients with major burn can cause changes in the response of propofol. Many other diseases can change the effect of anesthetic drugs in patients. The study of Bae and colleagues [1] would seem to reflect the increasing interest of anesthesiologists in clinical pharmacologic study. Korean anesthesiologists have recently focused on the clinical pharmacologic studies including pharmacokinetic/pharmacodynamic (PK/PD) modeling. The Korean Society for Intravenous Anesthesia changed its formal name to the Korean Society for Anesthetic Pharmacology in May 2008. Microemulsion propofol was developed in Korea and its induction and recovery characteristics have been evaluated [2].

Historically, modern anesthesia has slowly developed as a medical discipline since William Morton first administered ether to a patient. But anesthesia today stands out as the major primary medical specialty that routinely incorporates clinical pharmacology principles into patient care. Anesthesiologists have made major contributions to clinical pharmacology in the areas of physiological pharmacokinetics, PK-PD modeling and pharmacogenetics [3]. Physiologic pharmacokinetic models describe the time sequences of the measured blood and tissue drug concentrations by apportioning the cardiac output and hence the drug distribution, among the tissues with similar perfusion and drug solubility characteristics [4]. Brodie et al. [5] demonstrated that the effects of small doses of thiopental were terminated by redistribution from the site of action to other body tissues and not by metabolism. The physiologic pharmacokinetic model provides the first understanding of factors that contribute the variability in response to rapidly acting drugs. PK/PD modeling is the process of constructing a mathematical model to relate the time course of the dose to the concentration (PK) and the concentration to the effect (PD). Minto and Schnider [6] well summarized the enormous contribution of PK/PD modeling to advances in intravenous anesthesia. They said that PK/PD models have provided us with insight into the factors affecting the onset and offset of drugs' effects. The PK/PD model was postulated from the most important concept of the "effect compartment" model and this concept was developed from the data obtained from experiments where a neuromuscular-blocking agent was administered [7,8]. The data was modeled to integrate and characterized the lag time between the time course of the concentration of a drug and the time course of its measured effect. This concept was developed under the circumstances that patients are routinely and exhaustively monitored during anesthesia. This makes it easy to observe and quantify the effects of anesthetic drugs.

Anesthesia has been the benchmark for the development of new concepts and principles in clinical pharmacology. Using PK/PD modeling techniques from the early phases of clinical development has helped to define the characteristics of most drugs and specially those drugs that are intravenously administered. With the appropriate statistical methodology,

Corresponding author: Young-Cheol Woo, M.D., Department of Anesthesiology and Pain Medicine, Chung-Ang University Hospital, 224-1, Heukseok-dong, Dongjak-gu, Seoul 156-756, Korea. Tel: 82-2-6299-2584, Fax: 82-2-6299-2585, E-mail: wj12@naver.com

the effects of covariate factors have been identified and based on all this, rational dosing guidelines have been defined and later validated in routine clinical use [9]. For the point of view of the clinical pharmacologist, intravenously administered anesthetic drugs have concepts and lessons that are valuable for drug development. The intravenously administered hypnotic and opiate drugs that are used for producing anesthesia have fundamental characteristics that are applicable to all drug development. These characteristics include the 100% bioavailability and a precise knowledge of the administered drug dose, easy access to blood sampling, linear PKs, relatively rapid onset and offset, a profound degree of drug effect from awake to completely unconscious and the ability to directly record the drug effects as shown on an electroencephalogram [10]. Anesthesiologists have many advantages to gain knowledge and data for drug discovery, development, regulation, and utilization.

References

1. Bae JY, Choi DY, Woo CH, Kwak IS, Mun SH, Kim KM. The BIS and hemodynamic changes in major burn patients according to a slow infusion of propofol for induction. Korean J Anesthesiol 2011; 60: 161-6.
2. Kim KM, Choi BM, Park SW, Lee SH, Christensen LV, Zhou J, et al. Pharmacokinetics and pharmacodynamics of propofol microemulsion and lipid emulsion after an intravenous bolus and variable rate infusion. Anesthesiology 2007; 106: 924-34.
3. Avram MJ, Gupta DK, Atkinson AJ Jr. Anesthesia: a discipline that incorporates clinical pharmacology across the DDRU continuum. Clin Pharmacol Ther 2008; 84: 3-6.
4. Henthorn TK, Krejcie TC, Avram MJ. Early drug distribution: a generally neglected aspect of pharmacokinetics of particular relevance to intravenously administered anesthetic agents. Clin Pharmacol Ther 2008; 84: 18-22.
5. Brodie BB, Mark LC, Papper EM, Lief PA, Bernstein E, Rovenstine EA. The fate of thiopental in man and a method for its estimation in biological material. J Pharmacol Exp Ther 1950; 98: 85-96.
6. Minto CF, Schnider TW. Contributions of PK/PD modeling to intravenous anesthesia. Clin Pharmacol Ther 2008; 84: 27-38.
7. Hull CJ, Van Beem HB, McLeod K, Sibbald A, Watson MJ. A pharmacodynamic model for pancuronium. Br J Anaesth 1978; 50: 1113-23.
8. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther 1979; 25: 358-71.
9. Gambús PL, Trocóniz IF. Pharmacokinetic-pharmacodynamic modeling in anesthesia. Int Congr Ser 2001; 1220: 89-97.
10. Kern SE, Stanski DR. Pharmacokinetics and pharmacodynamics of intravenously administered anesthetic drugs: concepts and lessons for drug development. Clin Pharmacol Ther 2008; 84: 153-7.