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EDITORIAL

Drug interaction is the cornerstone of modern anesthesia practice

Chien-Kun TING *

Department of Anesthesiology, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan

*Corresponding author: Chien-Kun Ting, Department of Anesthesiology, Taipei Veterans General Hospital, National Yang-Ming University, 201 Section 2 Shi-Pai Road, Bei-Tou District, Taipei, 11211, Taiwan. E-mail: ckting2@gmail.com

In the study by Weber and Prasser published in this issue of *Minerva Anestesiologica*, 60 patients underwent elective otolaryngeal or ear surgery for investigating a propofol-sufentanil interaction model to determine the optimal concentration of either drug for adequate anesthesia and rapid recovery, by evaluating both clinical endpoints and electroencephalography findings.[1] They concluded that sufentanil has a dose-dependent synergistic effect on the clinically observed outcomes and parameters from three depths of hypnosis (DoH) devices (Bispectral Index [BIS], Narcotrend Index, and cAAI) in patients hypnotized with propofol.[1]

Anesthesiologists are required to have an in-depth knowledge of pharmacology;[2] we use the synergy between hypnotics and analgesics to suppress consciousness and nociception. Under general anesthesia, a set of desirable clinical endpoints should be achieved, including lack of awareness, lack of movement, adequate muscle relaxation, acceptable blood pressure, and body homeostasis maintenance. No single drug is universally satisfactory for achieving these endpoints. For practical purposes, anesthesia in the modern age involves the administration of at least two drugs — an opioid and a sedative hypnotic.[3] This concept of multiple drug use was first described by Lundy in 1926, who used the term balanced anesthesia.[4] Balanced anesthesia involves the use of desirable drug combinations by reducing the required doses of individual drugs to minimize the side effects. Currently, balanced anesthesia is one of the most worldwide used techniques for general anesthesia.

Drug interactions are usually considered in the dose or concentration domain, and there are many ways to study drug interaction. The dose–response relation curve is based on the standard sigmoid Emax model. In their study, Weber and Prasser used the modified Observer's Assessment of Alertness and Sedation Scale (mOAA/S)[5] to measure the clinical endpoints and defined loss of responsiveness to verbal command (LORverb) by the transition from mOAA/S level 3 to 2; noxious (painful) stimulation (LORnox), corresponding to mOAA/S level 0, served as the primary endpoint of this study. The mOAA/S Scale was firstly developed to measure the level of alertness in subjects who are sedated.[5] Probit regression analysis was used to determine the dose–response relation curve for the two different clinical endpoints.

There is experimental evidence showing that conscious recall of intraoperative events is only the tip of an iceberg.[6] Three DoH devices were used in the study of Weber and Prasser to avoid awareness and facilitate rapid recovery. The BIS index was first introduced in 1992 by Aspect Medical Systems. The main component of the BIS monitor is bispectral analysis, which evaluates the phase relations from a single channel EEG signal measured from the patient's forehead.[7] Although

BIS-guided anesthesia and ETAG-guided anesthesia may be equivalent with regard to avoidance of intraoperative awareness,[8] BIS-guided total intravenous anesthesia plays an important role in reducing the risk of intraoperative awareness.[9, 10] In 2000, Monitor Technik produced the Narcotrend monitor based on the concept described by Loomis *et al.*[11] The Narcotrend monitor classifies the state of anesthesia into five stages (A to F); they were further subdivided into three sub-stages by Kugler.[12] Analogous to BIS, the newer versions of the monitor also display the index value (0 to 100).[7] The first AEP commercial monitor was introduced by Danmeter in 2001. AEP-Monitor/2 is not only based on AEP, but also analyses the spectral EEG parameters.[7] Different DoH devices have different algorisms, which leads to a different index value; this is compatible with Weber and Prasser's finding that specific devices have their own dose–response curves.

Drug interactions can be described by shifts in dose–response curves, where one drug influences the dose–response curve for another drug. Weber and Prasser tried to analyses drug interaction using dose–response curves in the three DoH devices. Nonlinear regression was used to determine the curves. The method suggested by Hannam and Anderson[13] was applied to determine whether the interaction is synergistic or additive. If the curve was noted to shift to the left, it was considered to indicate synergy. The other approach to study interaction between two drugs is to plot dose pairs together to form a line which shows a particular level of effect. These isoeffect lines are called isoboles. Isobolograms can be easily constructed and analyzed. Numerous published studies have used this methodology, and their conclusions are comparable to those of studies using more complex methodologies; however, the limitation of isobolograms is that the result is only applicable to the effect level investigated. To gain a full understanding of the interaction between two drugs for all effect levels, it is possible to overlay a series of isoboles ranging from the minimal effect to the maximal effect attainable (Emax).[14]

The response surface is a three-dimensional graph with two drugs (A and B) on the horizontal *x* and *y* axes and the effect on the vertical *z* axis. The surface is based on the shift in dose-response curves and the isobologram; it describes effects for the complete set of doses for the endpoint in question. Responses may be either continuous, such as BIS and blood pressure, or quantal, such as sedation scale scores, awake/sleep, and movement/immobility. There was a breakthrough in response surface modeling after 2000, owing to not only the advancements in computing technology that made the complex calculation possible[15] but also the increasing demand for precise anesthesia. This concept was first introduced by Box and Wilson,[16] and was first introduced into the field of anesthesia by Greco *et al.*[14] in 1995. The response surfaces create models of all possible combinations of two or more drugs for a given effect. Further, they characterize the entire spectrum of the drug effect, which is an important advantage of this approach in anesthesia and clinical pharmacology. This approach reduces the complex physiology to a few mathematical elements.[2]

Drug interaction is the cornerstone of modern anesthesia practice. Understanding the synergism, additive effects, and even antagonism among anesthetics, especially hypnotics and opioids, may aid in making anesthesia more effective, minimizing side effects from the use of a single anesthetic, and improving the safety of patients. On the other hand, comprehending the underlying physiological mechanisms regulating the depth of hypnosis, by monitoring electroencephalography findings, can aid in formulating cost-effective and safer anesthetic protocols.

The study successfully addresses synergistic effect of sufentanil on the hypnotic effect of propofol both in their primary and second outcome by TCI effective site concentration (Marsh model). The findings provided some evidence that sufentanil could be beneficial in loss of consciousness of propofol, but problems with study design prevented the authors from fully addressing this issue. A comprehensive examination of opioid-propofol interaction requires a different study design. Future studies should consider reliable new methods such as response surface so that the findings can be generalized.

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