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Do we need to adjust the effect-site concentration of propofol in patients undergoing chemotherapy?

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Editorial

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Cancer is a leading cause of death not only in Korea but worldwide [1,2]. Colorectal cancer, in particular, is one of the most commonly diagnosed cancers, ranking third in terms of incidence and second in terms of mortality [2]. The incidence rate of colon cancer is highest in Europe, while the incidence rate of rectal cancer is highest in Eastern Asia [2]. The prevalence of colorectal cancer is expected to continue to increase with socioeconomic development, reflecting lifestyle changes, such as increased meat intake, excess body weight, and decreased physical activity [2]. Therefore, the number of patients with colorectal cancer that anesthesiologists encounter in clinical practice are expected to continue to increase.

Propofol, a γ-aminobutyric acid (GABA) receptor agonist, is one of the most used intravenous anesthetics due to its rapid induction and recovery rate and lower rate of adverse effects resulting from its favorable pharmacokinetic (PK) and pharmacodynamic (PD) profiles [3]. However, complications, such as hypotension and apnea, do occur. Previously, the *Korean Journal of Anesthesiology (KJA)* reported that fetal complications resulting from propofol administration occurred in 69.2% of all Korean medical disputes involving anesthesia, especially in cases of diagnostic gastrointestinal endoscopy and esthetic surgery [4]. Moreover, little is known about the PK/PD of propofol in patients with cancer who undergo chemotherapy. Chemotherapeutic drugs can cause hepatorenal or cardiopulmonary side effects and can alter sensitivity to anesthetics as a result of neurotoxic effects, which may cause changes in the PK/PD of propofol [5]. There is also a possibility of increased proliferation or metastasis of cancer cells by propofol through GABA or nuclear factor activation even though propofol is known to have antitumor and protective properties against cancer metastasis [6,7]. Such contradictory results may result from differences not only in cancer cell types but also propofol concentrations [7]. However, anesthesiologists use propofol for sedation and not for its anti-cancer effects. Therefore, it is worth investigating pharmacologic considerations of the effect-site concentration (Ce) of propofol for patients receiving colorectal cancer chemotherapy treatment based on an accurate PK/PD model. Increased knowledge regarding the appropriate amount of propofol to be administered for anesthetic depth in cancer patients will improve patient safety and outcomes.

The current edition of the KJA includes a study conducted by Ki et al. [8] investigating the Ce of propofol for loss of verbal contact and loss of consciousness (LOC) using the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) score. During anesthesia induction, the Ce of propofol was increased by target-controlled infusion (TCI) using the Schnider model until the MOAA/S score reached zero. No differences were seen in the Ce of propofol in terms of the MOAA/S score, sedation time, or bispectral index in patients with colorectal cancer receiving chemotherapy. Based on non-linear

mixed-effects modeling, the predicted propofol concentrations that would produce a 50% probability of moderate sedation (MOAA/S ≤ 3) and deep sedation (MOAA/S ≤ 1) in patients receiving chemotherapy (2.25 and 3.11 μg/ml, respectively) and not receiving chemotherapy (2.12 and 2.66 μg/ml, respectively) were proposed.

Some studies have shown increased sensitivity to propofol in patients receiving chemotherapeutic agents for breast cancer; however, these studies either focused on the neurotoxicity of neoadjuvant agents or did not include population PK/PD analyses [9,10]. In addition, Ki et al. [8] suggested that the primary explanations for the differences in the study results were that the main therapeutic agents for breast cancer (docetaxel or doxorubicin) and colorectal cancer (oxaliplatin + leucovorin + 5-fluorouracil combination) and the treatment durations are different. However, the incidence of neurotoxicity after the use of chemotherapeutic drugs for colorectal cancer is as high as 84.3% [11]. This means that the Ce of propofol for adequate sedation depends not only on sensitivity but also on PK/PD properties influenced by numerous factors, including certain patient characteristics and conditions (e.g., sex, age, weight, or cardiac output) [12,13]. Patients with cancer usually experience significant weight loss and complications of chemotherapy, such as anemia, hypoalbuminemia, and hepatorenal or cardiac dysfunction [12]. In clinical practice, the TCI model of propofol is based on the PK/PD profiles of healthy individuals. Therefore, for the safe use of propofol in the colorectal cancer population, a PK/PD model should be adequately evaluated for this population [14].

According to the population PK/PD model for cancer patients undergoing major lung surgery, no modification of the propofol dosage was necessary when the Schnider model was used for the TCI of propofol [12]. In other words, the changes in covariates do not significantly affect the PK/PD profiles of propofol, even with chemotherapy, and the existing model can be used for TCI. Similarly, Ki et al. [8] found no significant differences in the Ce of propofol in terms of LOC using the Schnider model between patients who received chemotherapy and those who did not. The only factor that showed some differences in terms of the Ce of propofol was gender (men, 2.67 ± 0.41 vs. women, 2.45 ± 0.37 μg/ml) according to the PD analysis, and the authors thus recommended that the dose of propofol not be reduced in patients with colorectal cancer undergoing chemotherapy.

In conclusion, there are no significant differences in the Ce of propofol between the patients with colorectal cancer who are and are not receiving chemotherapy. These findings, which were determined using scientific population PK/PD analysis, may be used to improve the safe clinical application of the TCI of propofol.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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