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Remimazolam: another option for induction of general anesthesia?

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Editorial

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For several decades after its introduction in 1934, thiopental was the most widely used intravenous anesthetic induction agent. However, propofol replaced thiopental in the 1990s owing to its various comparative advantages, including quicker recovery, shorter context-sensitive half-time, and antipruritic and antiemetic effects. Target-controlled infusion pumps with pharmacokinetic models and electroencephalogram-based anesthesia depth-monitoring devices have accelerated this trend. Numerous studies have provided further evidence for the safety and efficacy of propofol in various clinical situations [1–4].

Thirty years after the introduction of propofol, remimazolam, an ultra-short-acting benzodiazepine, was introduced as a novel intravenous anesthetic agent [5]. Remimazolam acts on the inactive metabolites by non-specific tissue esterases. Because remimazolam has a high clearance, small steady-state volume of distribution, and short context-sensitive half-time [5], it may not require dose adjustments in patients with renal or hepatic impairment [6]. Additionally, remimazolam has advantages over propofol, particularly in terms of safety, including less hemodynamic instability and respiratory depression, no pain on injection, and a known reversible agent, flumazenil [7–9].

However, many hurdles must be overcome before remimazolam can be widely used for general anesthesia. First, although remimazolam has been approved for general anesthesia in Japan and South Korea, it has not yet been approved for this purpose in other countries [5]. Second, commercially available infusion pumps and pharmacokinetic models for the target-controlled infusion of remimazolam are limited. Third, anesthesia depth monitoring indices, such as the bispectral index (Medtronic, Ireland) or patient state index (Masimo, USA), are not well correlated with loss of consciousness in general anesthesia with remimazolam [10,11]. Fourth, interactions with other drugs used for general anesthesia, particularly opioid analgesics, have not been studied sufficiently. Fifth, few studies have been conducted on the clinical outcomes after general anesthesia using remimazolam [12–15]. Sixth, no consensus has been reached on the doses of remimazolam for induction and maintenance of general anesthesia.

However, studies have been conducted recently to determine the induction dose of remimazolam for general anesthesia. Dai et al. [9] conducted a study to determine the appropriate single bolus injection dose of remimazolam (0.2, 0.3, or 0.4 mg/kg) for anesthesia induction within 1 min. They randomly assigned 189 patients to four groups (the remimazolam 0.2, 0.3, and 0.4 mg/kg groups and the propofol group) and reported a 94% success rate for loss of consciousness in the remimazolam 0.3 mg/kg group. In another study, Chae et al. [11] used a parametric time-to-event model to estimate the effective dose of remimazolam required to achieve a 95% success rate (ED95) for loss of consciousness within 5 min. They randomly assigned 120 patients to six different dose groups (0.02, 0.07, 0.12, 0.17, 0.22, and 0.27 mg/kg) and found the estimated ED95 to be 0.33, 0.25, 0.19, and 0.14 mg/kg for patients aged 20, 40, 60, and 80 years, respectively.

From the results, they proposed the following induction doses for remimazolam: 0.25–0.33 for patients aged < 40 years, 0.19–0.25 for those aged 40–60 years, and 0.14–0.19 mg/kg for those aged 60–80 years.

In this issue of the *Korean Journal of Anesthesiology*, another study aimed to determine the induction dose of remimazolam for general anesthesia was reported by Oh et al. [16]. Unlike previous studies, the authors of this study determined the ED95 of remimazolam for loss of consciousness within 3 min using the biased coin up-and-down method. This method is a type of sequential design for clinical trials that enables accurate estimation of the effective dose for a specific success rate without repeatedly exposing subjects to the same dose [17]. They enrolled 40 patients each in the young (20–39 years), middle-aged (40–59 years), and elderly (60–79 years) groups and found the ED95 of remimazolam for loss of consciousness within 3 min to be 0.37 mg/kg (95% CI [0.28, 0.39]) in the young group, 0.37 mg/kg (95% CI [0.27, 0.39]) in the middle-aged group, and 0.25 mg/kg (95% CI [0.20, 0.29]) in the elderly group. The discrepancies in the ED95 between the studies conducted by Chae et al. [11] and Oh et al. [16] in the middle-aged group (0.19–0.25 vs. 0.27–0.39 mg/kg) and elderly group (0.14–0.19 vs. 0.20–0.29 mg/kg) may be due to differences in the maximum observation period for loss of consciousness between the studies (5 min for Chae et al. vs. 3 min for Oh et al.). In general, slower induction with a smaller dose of induction agent is purposed for reducing side effects. However, it is notable that none of the patients experienced hypotension or bradycardia that required rescue medications during the 3 min observation period in the study conducted by Oh et al. [16].

Although remimazolam has potential advantages over propofol, the current evidence is still insufficient, especially regarding general anesthesia. Therefore, whether remimazolam could be widely used for general anesthesia in the future remains uncertain. Well-designed clinical studies and reports of clinical experiences are needed to confirm the safety and efficacy of remimazolam for general anesthesia in various clinical situations.

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Conflicts of Interest

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

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