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EDITORIAL

Remimazolam: a new string to the TIVA bow

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Remimazolam is a member of the benzodiazepine family with a chemical structure and pharmacological action similar to that of midazolam and, like remifentanil, is rapidly metabolized [1]. Induction with propofol produces the potential for "Can't Intubate, Can't Ventilate (CICV)" scenarios as there is no effective antagonist. In contrast, remimazolam action can be antagonized by flumazenil producing additional safety. Remimazolam has the potential broaden/adds new options to TIVA. In this Editorial, I outline the advantages and problems of remimazolam.

Pharmacological characteristics

Remimazolam exerts its sedative effects by facilitating the binding of GABA to $GABA_A$ receptors at the benzodiazepine binding site. Indeed, remimazolam binds with high affinity to the benzodiazepine binding site of the rat brain $GABA_A$ receptor, while the main metabolite, CNS7054, bound with 300–400-fold lower affinity [1]. Remimazolam has threefold higher systemic clearance than midazolam, and a steady state distribution volume of 37.3 L, terminal half-life of 0.92 h, and mean residence time of 0.57 h [2]. U.S. phase I pharmacokinetic trials demonstrated that the simulated context-sensitive half-time of remimazolam is 7–8 min after 2-h infusion; this is much shorter than midazolam [2].

Beneficial actions

Antinociception

Although midazolam exerts analgesic effects via the κ-opioid receptor [3], there is no data showing remimazolam interaction with opioid receptors. Structural similarity is suggestive of similar κ-opioid receptor profiles. Benzodiazepines in general are known to enhance opioid analgesia [4], so it is not unreasonable. Bevans and colleagues [5] reported that inhaled remimazolam potentiated inhaled remifentanil-induced analgesia in mice using a tail flick test. Moreover, Kops et al. [6] reported that both remimazolam and midazolam showed a higher synergy for remifentanil (94% and 98%, respectively) compared to propofol (61%) in monkeys. An enhancing effect of remimazolam on opioid analgesia has been shown in the clinical setting by Dao and colleagues [7] who reported that patients with remimazolam sedation required significantly less fentanyl for analgesia than those with midazolam sedation.

Anti-inflammatory effects

Liu and colleagues [8] determined whether remimazolam diminished lipopolysaccharide (LPS)-induced inflammation both in vitro and in vivo. They found that survival was significantly longer in mice with remimazolam and that remimazolam significantly reduced LPS-increased inflammatory mediators, such as TNF-α, IL-6, and IL-1β. From their data, they speculated that the anti-inflammatory effects of remimazolam may be due to inhibition of mitogen-activated protein kinase (MAPK) signal pathway and Ras-related protein Rab-5A (Rab5a)-related Toll-like receptor 4 (TLR4) expression at cell surface in response to LPS. Fang and colleagues [9] used a sepsis-associated acute liver injury (SALI) rat model which involved treatment with LPS and galactosamine (aggravation of LPS-induced liver injury) to determine anti-inflammatory effects of remimazolam. They found that remimazolam mitigated SALI and alleviated inflammation and elevation of p38 MAPK phosphorylation. These effects were reversed by a peripheral benzodiazepine antagonist, PK11195. There are no current reports on the anti-inflammatory effects of remimazolam in the clinical setting.

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Neuroprotective effects

Shi and colleagues [10] used a rat model of middle cerebral artery occlusion (MCAO) with focal transient cerebral ischemia/reperfusion (I/R) injury to determine neuroprotective effects of remimazolam. They found that remimazolam could alleviate MACO-induced neurological dysfunction, infarct volume, and cortical neuronal damages. Neuroprotection with remimazolam may be due to inhibition of nucleotide-binding oligomerization domain-like receptors pyrin domain containing 3 (NLRP3) inflammasome pathway followed by suppression of pyroptosis and further inflammatory cascades.

Anti-tumor effects

Although there are no reports clearly indicating anti-tumor effects of remimazolam, several articles are suggestive. Midazolam has been reported to pose anti-tumor activity against various tumors [11–14]. In addition, the anti-tumor actions were antagonized by flumazenil in neuroglioma, lung carcinoma, and melanoma [11, 12] or by PK11195 in lung cancer, breast cancer, and pancreatic ductal adenocarcinoma [13, 14]. As anti-tumor actions of midazolam were antagonized by benzodiazepine antagonists, remimazolam is likely to exert similar anti-tumor actions.

Prevention of "Can't Intubate, Can't Ventilate (CICV)"

A situation that anesthesiologists most wish to avoid is "Can't Intubate, Can't Ventilate (CICV)" during induction of anesthesia. Could CICV be avoided with the advent of sugammadex? To address CICV, rapid recovery of spontaneous respiration is essential. In CICV situation, sugammadex should be promptly administrated to antagonize rocuronium-induced neuromuscular blockade. However, as not only neuromuscular blockade but also sedatives and opioids also produce a prolonged respiratory depression, reversal of sedatives and opioids is required to fully restore respiratory activity [15]. Although opioid actions can be reversed by naloxone, no antagonist was available for short-acting anesthetic agents for the induction of anesthesia before advent of remimazolam. With flumazenil reversible remimazolam actions a family of reversal agents are available to mitigate CICV scenarios.

Hemodynamics

A Japanese phase IIb/III trial for remimazolam demonstrated that hypotensive adverse drug reaction was significantly lower in patients with remimazolam (20.0–24.0%) compared with patients with propofol (49.3%) [16]. In ASA III patients hypotensive adverse reactions were 41.9% and 67.7% at induction doses of remimazolam of 6 and 12 mg/kg/h, respectively, while propofol causes hypotension in up to 75% of patients [17]. Remimazolam anesthesia is noninferior to inhalation anesthesia in terms of hemodynamics. Song et al. [18] reported that the occurrence of intraoperative hypotension was comparable to both remimazolam TIVA ($n = 84$) and desflurane anesthesia ($n = 84$) in patients aged 19–65 years undergoing elective laparoscopic cholecystectomy or robotic gynecologic surgery. When compared with sevoflurane, Lee and colleagues [19] found that remimazolam anesthesia was associated with significantly less frequent use of vasopressors.

Adverse reactions

Anaphylaxis

There have been several case reports of anaphylactic shock associated with remimazolam [20, 21]. Some cases have resulted in cardiac arrest [20, 21]. The frequency of anaphylactic shock with remimazolam is not yet known.

Postoperative cognition

Although the context-sensitive half-time of remimazolam is similar to that of propofol at the 2-h infusion and lower with longer infusions [22], recovery of BIS, and cognitive function after termination of anesthetic infusion is faster with propofol than remimazolam [16]. Song and colleagues [18] compared quality of recovery between remimazolam and desflurane anesthesia and found that a time to extubation, cognitive recovery, and to discharge from postoperative care unit (PACU) are significantly longer in the remimazolam group than in the desflurane group. However, when flumazenil is used, times to emergence from anesthesia and the length of PACU stay have also been reported to be faster than with propofol anesthesia even in cirrhotic patients [23]. Why does slow cognitive recovery occur with remimazolam anesthesia? In general, it is known that benzodiazepines increase the risk of postoperative delirium [24]. Zhou et al. [25] studied the effects of remimazolam on various cognitive tests in mice. They found that remimazolam declined cognitive function in a dose-dependent manner. The results suggest that the mechanism of remimazolam-induced cognitive dysfunction may be due to activation of glutamate receptors and Ca–calmodulin-dependent protein kinase (CAMK) II. The increases in intracellular Ca^{2+} induce neuronal apoptosis. Another contributing factor is the accumulation of amyloid-β plaques in the brain due to abnormal phosphorylation of tau protein. Although volatile inhaled anesthetics also induced amyloid-β accumulation [26], cognitive

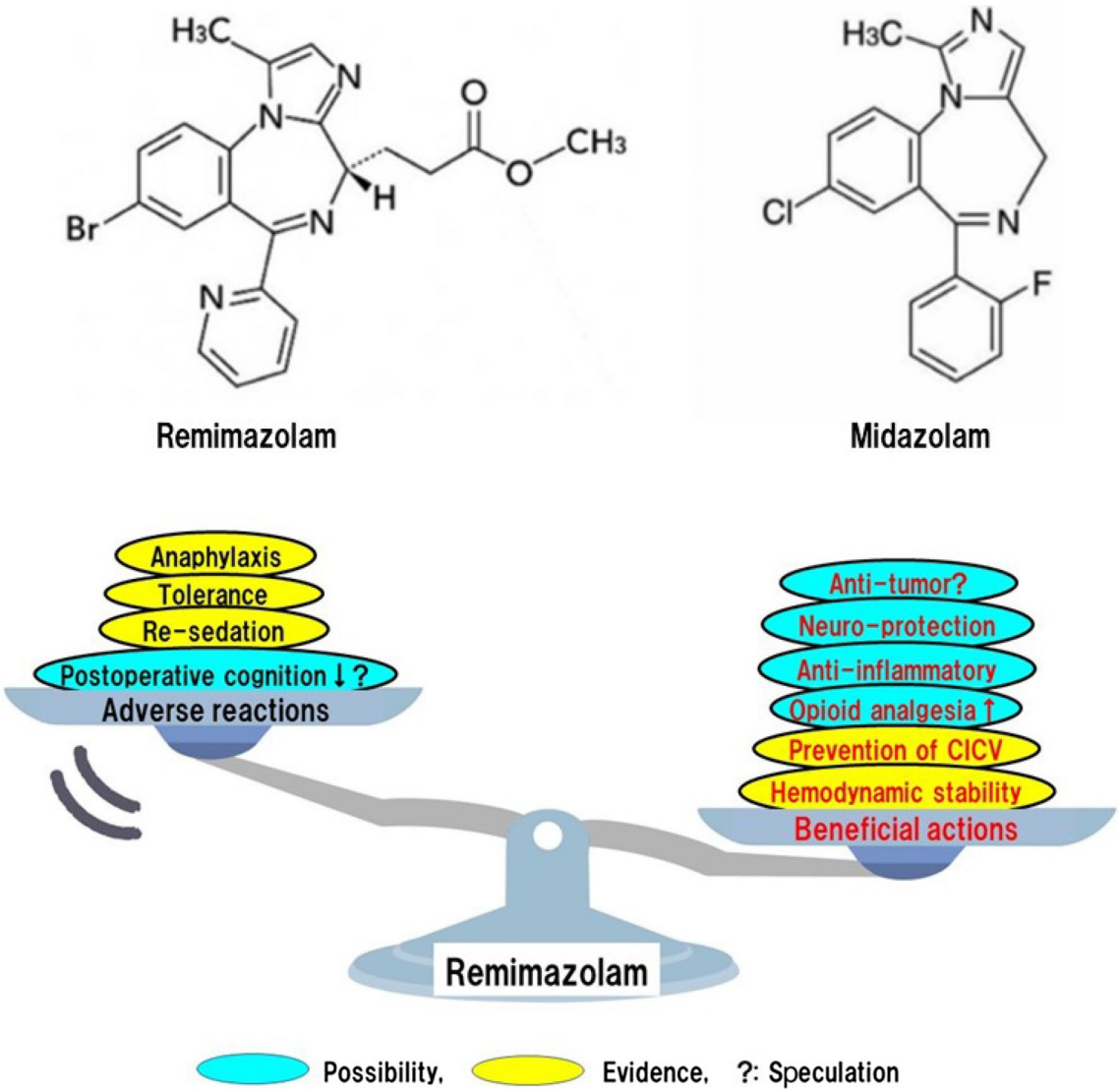

Fig. 1 Structures of midazolam and remimazolam (from Fig. 1 in Ref. [20]), and balance of possible beneficial and adverse actions of remimazolam

recovery is rapid after desflurane anesthesia [18]. Thus, it is doubtful whether amyloid-β accumulation alone may contribute to the mechanism. In a prospective cohort study of cardiovascular surgical patients. Aoki et al. [27] showed no difference in the incidence of POD between anesthesia with and without remimazolam. It is difficult to conclude using only this report that the incidence of POD with remimazolam is comparable to other anesthetic agents; future studies are required.

Tolerance to remimazolam in patients with existing benzodiazepine medication

Tolerance to benzodiazepines occurs for many of their effects, especially for sleep with regular use [28]. Indeed, there are several reports showing difficulty in maintaining anesthesia with remimazolam [29, 30]. Remimazolam should be avoided in chronic benzodiazepine users (See Fig. 1).

Remimazolam re-sedation after flumazenil administration

Using pharmacokinetic simulations, Masui [31] explains that the risk of re-sedation after remimazolam is antagonized by flumazenil. If a larger bolus of flumazenil is administered, there is a risk of reappearance of remimazolam sedation due to competitive mechanism of action. A larger bolus of flumazenil strongly antagonizes the action of remimazolam immediately after the bolus. However, if the residual remimazolam concentration is high, the reversal effect may

disappear 10 min after the bolus dose of flumazenil. In addition, a decrease in total clearance of remimazolam is another risk for reappearance. Patients with lower clearance have a slower decline in remimazolam concentration after the end of remimazolam infusion, resulting in higher residual concentrations thereafter. Reduction in hepatic blood flow may also be a risk as remimazolam is primarily metabolized by carboxylesterase 1 in the liver. Indeed, there are a few reports [32] regarding re-sedation after remimazolam anesthesia followed by reversal of flumazenil. Therefore, pharmacokinetic simulation with monitoring clinical symptoms after the termination of remimazolam infusion may be useful to predict the time course of residual effects and the possibility of re-sedation.

In this editorial, I have introduced the beneficial–adverse actions balance for remimazolam. Further studies are required, and these will be facilitated by wider availability and use.

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Data Availability There are no data obtained for this report.

Declarations

Conflict of interest Professor Hirota has received a lecture fee three times from Mundipharma K.K, remimazolam distributor in Japan.

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