Texila International Journal of Public Health
Special Issue-2024
DOI: 10.21522/TIJPH.2013.SE.24.05.Art011

In-Silico Molecular Interaction and Pharmacokinetic Evaluation of Remimazolam and Major Intravenous Anesthetics Targeting GABAA Receptors

Jaganathan Ramakrishnan[1]*, Manjupriya Jothi[2], Thamizhmathi Thangaraju[3]

[1]*Center for Global Health Research, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Chennai – 602 105, Tamil Nadu, India*

[2]*Centre for Nanoscience and Nanotechnology, Department of Physics, Bharathidasan University, Tiruchirappalli - 620 024, Tamil Nadu, India*

[3]*Department of Anaesthesiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Chennai – 602 105, Tamil Nadu, India*

Abstract

This study investigates the molecular interactions and pharmacokinetic properties of five intravenous anaesthetics Remimazolam, Midazolam, Propofol, Thiopental, and Etomidate with the γ-Aminobutyric acid type A ($GABA_A$) receptor, a key mediator of inhibitory neurotransmission in the central nervous system. Using molecular docking analysis, we evaluated the binding affinities of these drugs to the $GABA_A$ neurotransmitter receptor. Remimazolam emerged as a promising candidate with a docking score of -6.9 kcal/mol, demonstrating strong and stable interactions with critical receptor residues such as THR96 and GLN65. Although Midazolam exhibited a slightly superior docking score of -7.1 kcal/mol, Remimazolam's pharmacokinetic profile offers distinct advantages, including rapid onset, short duration of action, and a favourable safety profile with minimal risk of hepatotoxicity and skin sensitization. In comparison, Propofol, Thiopental, and Etomidate showed weaker binding affinities and raised safety concerns. These findings suggest that Remimazolam is a competitive and safer alternative to existing intravenous anaesthetics, particularly in outpatient settings and procedures requiring efficient anaesthetic management. This study contributes valuable insights into the clinical application of Remimazolam, reinforcing its potential as an effective choice in the realm of intravenous anaesthesia.

Keywords: *Anaesthesia, ADMET, $GABA_A$ Receptor, Midazolam, Molecular Docking, Neurotransmitter, Remimazolam.*

Introduction

The γ-Aminobutyric acid type A ($GABA_A$) receptor is a critical mediator of inhibitory neurotransmission in the central nervous system, serving as the primary target for various intravenous anaesthetics that enhance GABAergic signaling to induce sedation, hypnosis, and general anaesthesia [1, 2]. Recent research highlights important considerations in dental anaesthesia, including dentists' knowledge and practices regarding general anaesthesia for children, the effectiveness of local anaesthesia with and without adrenaline in cardiac patients, and the implications of performing dental impactions under general anaesthesia [3–5]. Understanding the interaction between anaesthetic agents and the $GABA_A$ receptor is essential for optimizing anaesthetic efficacy and safety. Among the drugs targeting this receptor, Remimazolam is a novel benzodiazepine that has gained

Received: 16.09.2024 ***Accepted: 08.10.2024*** ***Published on: 10.12.2024***

Corresponding Author: rjaganphy@gmail.com

significant attention due to its rapid onset and ultra-short duration of action, largely attributed to its rapid metabolism by tissue esterase [6, 7]. This novel intravenous anaesthetic is specifically designed for procedural sedation, general anaesthesia, and intensive care, offering a faster and more predictable recovery compared to other benzodiazepines, such as Midazolam [8, 9]. Furthermore, Remimazolam maintains an advantageous safety profile when compared to other anaesthetics like Propofol, making it an attractive option for outpatient settings and short medical procedures. The meta-analysis by Liyun Dong et al (2024). supports our findings by confirming that Remimazolam offers similar anaesthetic efficacy to Propofol while providing a superior safety profile, especially in elderly patients. This aligns with our study's conclusion that Remimazolam is an effective and safer alternative to traditional intravenous anaesthetics [10]. And the study by Hoshino et al (2024). reveals that Remimazolam enhances GABAergic inhibitory transmission in the spinal dorsal horn, resulting in significant analgesia in inflammatory pain. This suggests that Remimazolam may serve not only as a sedative but also as an effective spinal analgesic, supporting its broader clinical utility [7, 11–13].

Despite its promising pharmacokinetic properties, a detailed comparative analysis of Remimazolam's binding affinity with the $GABA_A$ receptor relative to other widely used intravenous anaesthetics such as Propofol, Thiopental, Etomidate, and Midazolam has not been thoroughly investigated [14, 15]. This study aims to fill this gap by performing molecular docking analysis using AutoDock Vina to evaluate the binding interactions of Remimazolam with the $GABA_A$ receptor. The results will be compared with the binding affinities of Propofol, Thiopental, Etomidate, and Midazolam, providing insights into the relative efficacy of these anaesthetics at the molecular level.

Materials and Methods

Molecular Docking

The study was conducted using molecular docking simulations to evaluate the binding affinity of Remimazolam and other selected intravenous anaesthetics with the $GABA_A$ receptor. The crystal structure of the $GABA_A$ receptor (PDB ID: 4COF) was retrieved from the Protein Data Bank (www.rcsb.org), ensuring that the selected structure was suitable for docking studies, particularly regarding the resolution and the presence of the active site [16, 17]. For the ligands, the 3D structures of Remimazolam, Propofol, Thiopental, Etomidate, and Midazolam were obtained from the PubChem database in SDF format. Each ligand structure was subjected to energy minimization using Chem3D with MM2 calculation to ensure an optimal conformation for docking, and the structures were saved in PDB format [18, 19]. Before the docking, both ligands and receptor structures were prepared using AutoDockTools (ADT). The target structure was prepared for docking by removing water molecules, adding polar hydrogens, and assigning Kollman charges to the protein using AutoDockTools [20]. Nonpolar hydrogens were merged, and the rotatable bonds in the ligand were defined to allow flexibility during docking. Both the ligand and target structures were then converted to PDBQT format, which includes atomic coordinates, partial charges, and atom types necessary for the AutoDock Vina docking algorithm. The molecular docking simulations were performed using AutoDock Vina, a widely used tool for predicting the binding modes and affinities of ligands to their target receptor. The grid box was carefully defined around the active site of the $GABA_A$ receptor, covering the relevant binding pocket where these anaesthetics are known to interact.

Each ligand was docked to the $GABA_A$ receptor multiple times to ensure accuracy and reproducibility of the results. The docking

output provided binding energy values, with the best binding pose for each ligand being selected based on the lowest binding energy. These poses were further analyzed to understand the nature of the interactions between the ligands and the receptor, focusing on hydrogen bonds, hydrophobic interactions, and other relevant molecular interactions. Visualization of these interactions was done using PyMOL and Discovery Studio, generating both 2D interaction diagrams and 3D representations of the ligand-receptor complexes [21, 22].

The binding affinities of Remimazolam were compared with those of Propofol, Thiopental, Etomidate, and Midazolam to determine which drug exhibited the strongest interaction with the $GABA_A$ receptor. This comparative analysis aimed to provide insights into the potential clinical efficacy of Remimazolam relative to established anaesthetics, contributing valuable information to the field of anaesthesiology.

Pharmacokinetic Properties/ADMET

To comprehensively assess the pharmacokinetic properties of Remimazolam, Propofol, Thiopental, Etomidate, and Midazolam, we conducted an ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis using the pkCSM tool, a computational method that predicts the ADMET characteristics of small molecules based on their chemical structure, providing valuable insights into their pharmacokinetic behaviour, potential toxicity, and overall drug-likeness [23–25]. Absorption properties, including water solubility, human intestinal absorption, and Caco-2 permeability, help determine a drug's absorption efficiency and bioavailability. Distribution parameters, such as volume of distribution (VDss), blood-brain barrier (BBB) permeability, and CNS permeability, indicate how widely a drug disperses throughout the body and its ability to penetrate the central nervous system. Metabolism predictions focus on whether the drug is a substrate or inhibitor of key cytochrome P450 enzymes (CYPs), essential for predicting drug-drug interactions and metabolic stability. Excretion properties, including total and renal clearance, reveal how quickly a drug is eliminated from the body, informing its half-life and dosing frequency. Toxicity predictions assess risks of hepatotoxicity, skin sensitization, and adverse effects such as cardiotoxicity or mutagenicity, ensuring the safety of the drug for long-term use.

Results

Docking Scores

The molecular docking analysis revealed significant differences in the binding affinities of the five intravenous anaesthetics to the $GABA_A$ receptor, with scores ranging from -4.7 to -7.1 kcal/mol (Figure 1 and Table 1). Midazolam exhibited the strongest binding affinity with a docking score of -7.1 kcal/mol. This high score suggests that Midazolam forms a particularly stable and effective interaction with the $GABA_A$ receptor, supporting its widespread use and clinical efficacy. Remimazolam followed with a docking score of -6.9 kcal/mol, indicating a strong binding affinity as well, which aligns with its rapid onset and short duration of action. The competitive binding affinity of Remimazolam underscores its potential as a viable alternative to Midazolam in various clinical settings.

Table 1. Docking Scores of Selective Anaesthetic Drugs with GABAA Receptor and the Interacted Amino Acids

Sl. No	Anaesthetic Drug	PubChem ID	Canonical SMILES	Docking Score (kcal/mol)
1.	Remimazolam	9867812	CC1=CN=C2N1C3=C(C=C(C=C3)Br)C(=NC2CCC(=O)OC)C4=CC=CC=N4	-6.9
2.	Propofol	4943	CC(C)C1=C(C(=CC=C1)C(C)C)O	-5.2

3.	Thiopental	3000715	CCCC(C)C1(C(=O)NC(=S)NC1=O)CC	-4.7
4.	Etomidate	667484	CCOC(=O)C1=CN=CN1[C@H](C)C2=CC=CC=C2	-5.1
5.	Midazolam	4192	CC1=NC=C2N1C3=C(C=C(C=C3)Cl)C(=NC2)C4=CC=CC=C4F	-7.1

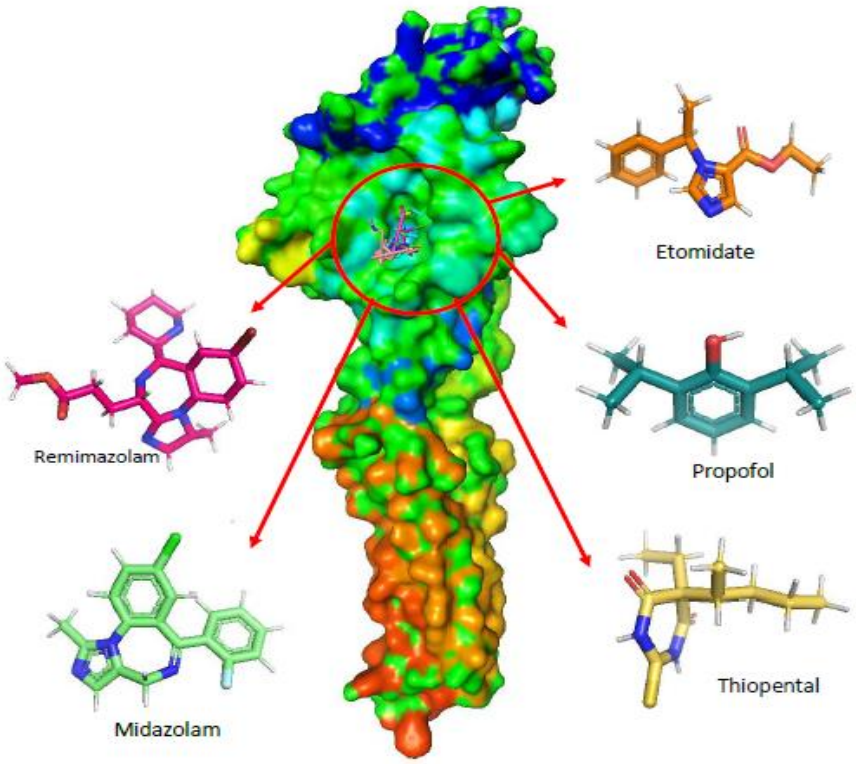

Figure 1. Superimposed Structure of Selective Anaesthetic Drugs in the Active Site of $GABA_A$ Receptor, Obtained from the Molecular Docking Analysis

In contrast, Propofol and Etomidate displayed moderate binding affinities with docking scores of -5.2 kcal/mol and -5.1 kcal/mol, respectively. These scores reflect effective receptor interaction, though not as pronounced as that of Midazolam and Remimazolam. Propofol's moderate affinity is consistent with its established efficacy in anaesthesia, while Etomidate's score supports its use in scenarios requiring stable hemodynamic conditions. Thiopental had the lowest docking score of -4.7 kcal/mol, indicating weaker receptor interaction compared to the others. Despite its lower binding affinity, Thiopental remains effective due to its rapid induction properties and historical clinical use.

Intermolecular Interactions

The analysis of intermolecular interactions (Figure 2 and Table 2) provides deeper insights into the nature of binding beyond the docking scores. Midazolam formed several key hydrogen bonds and electrostatic interactions with residues such as THR96 (O) and ASP101 (OD2). The presence of halogen bonding with THR96 (O) further stabilizes the interaction, contributing to its highest docking score. In comparison, Remimazolam engaged in multiple hydrogen bonds with residues like THR96 (O) and GLN65 (H21), as well as hydrophobic interactions with TYR97. This combination of interactions supports its high binding affinity and effective receptor engagement.

Table 2. Intermolecular Interactions between the Selective Anaesthetic Drugs and Active Site Amino Acids of GABAA

Drug	Ligand atom···Residue	Category	Distance (Å)
Remimazolam	LIG(H)···THR96(O)	Hydrogen Bond	2.0244
	LIG(OH)···THR96(O)	Hydrogen Bond	2.33725
	LIG(C)···GLN65(H21)	Hydrogen Bond	2.77301
	LIG(O)···THR96(C)	Hydrogen Bond	3.76703
	LIG(Br)···TYR97	Hydrophobic	5.20162
Propofol	LIG(C)···ILE130	Hydrophobic	3.80912
	LIG(C)···VAL93	Hydrophobic	4.62266
	LIG(C)···LEU128	Hydrophobic	4.65115
	LIG···LEU128	Hydrophobic	5.43322
	LIG(C)···PHE98	Hydrophobic	4.83567
	LIG(C)···PHE98	Hydrophobic	4.31023
	LIG(C)···TYR126	Hydrophobic	5.05397
Thiopental	LIG(O)···SER104(C)	Hydrogen Bond	3.59578
	LIG(C)···ILE130	Hydrophobic	5.3088
	LIG(C)···PHE63	Hydrophobic	4.35429
	LIG(C)···PHE98	Hydrophobic	4.41248
	LIG(C)··· PHE98	Hydrophobic	4.65007
Etomidate	LIG(C)···VAL106	Hydrophobic	4.65748
	LIG(C)···LEU128	Hydrophobic	4.62239
	LIG(C)···ILE130	Hydrophobic	4.25961
	LIG(C)···VAL106	Hydrophobic	4.63774
Midazolam	LIG(Cl)···LYS112(N)	Electrostatic	3.36593
	LIG(H)···THR96(O)	Hydrogen Bond	2.30372
	LIG(H3)···ASP101(OD2)	Hydrogen Bond	2.51723
	LIG(F)···GLN65(HE21)	Hydrogen Bond	2.99569
	LIG(F)···THR96(O)	Halogen	3.47663
	LIG(F)···LEU128	Hydrophobic	5.22568
	LIG(F)···PHE63	Hydrophobic	5.24381

Propofol primarily interacted through hydrophobic contacts with residues like ILE130 and LEU128. Although these interactions are effective, they are less diverse compared to the hydrogen bonds seen in Midazolam and Remimazolam. Similarly, Etomidate relied on hydrophobic interactions, though its overall binding profile was less robust than that of Remimazolam and Midazolam. Thiopental showed a mix of hydrogen bonds with SER104 (C) and hydrophobic interactions with residues like PHE98, but its overall interaction profile was weaker, aligning with its lower docking score.

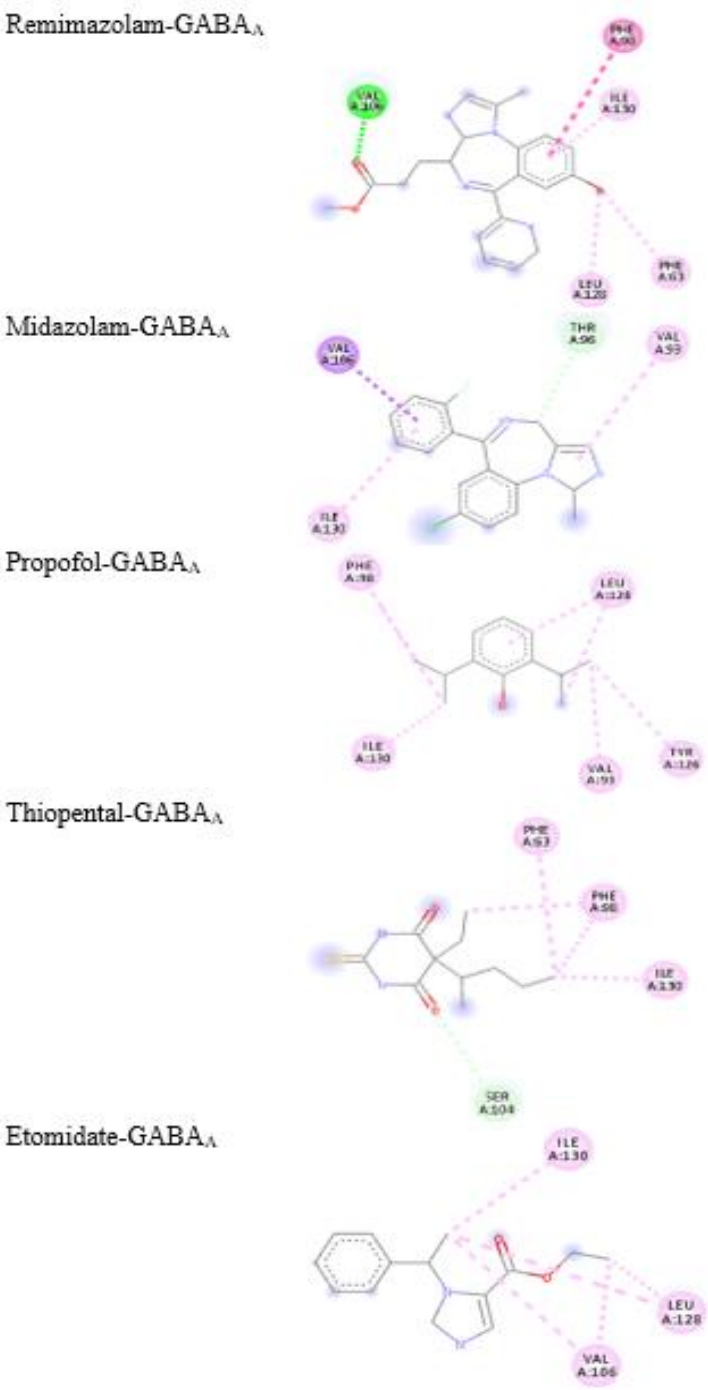

Figure 2. Intermolecular Interactions between Selective Anaesthetic Drugs with the Active Site Residues of GABA$_A$ Receptor

ADMET Profiling

The ADMET profiling (Table 3) provides a comparative analysis of the pharmacokinetic properties and toxicity profiles of the anaesthetics. Remimazolam and Midazolam exhibit high human intestinal absorption (HIA) percentages, with Remimazolam at 97.6% and Midazolam at 97.1%, suggesting good oral bioavailability. Propofol, Thiopental, and Etomidate also show high HIA, though slightly lower than Remimazolam and Midazolam.

In terms of solubility, Remimazolam is less soluble compared to Propofol and Etomidate, but its solubility remains within an acceptable range for intravenous use. The volume of distribution (VDss) is notably high for

Remimazolam (0.439 log L/kg) and Midazolam (0.582 log L/kg), indicating extensive distribution in the body. The blood-brain barrier (BBB) permeability is also favourable for both drugs, with Remimazolam and Midazolam showing good CNS penetration.

Table 3. Predicted ADMET Properties of Selective Intravenous Anaesthetics using pkCSM

Property	Remimazolam	Midazolam	Propofol	Thiopental	Etomidate
Absorption					
Solubility	-3.229	-3.362	-4.019	-2.514	-4.134
HIA (%)	97.599	97.132	91.115	93.977	96.511
Caco-2 Permeability	0.657	1.613	1.564	1.222	1.323
Distribution					
VDss (log L/kg)	0.439	0.582	0.703	-0.123	0.224
BBB Permeability	-1.143	0.203	0.497	-0.122	0.425
CNS Permeability	-2.142	-1.418	-1.365	-2.99	-1.804
Metabolism					
CYP2D6 Substrate	No	No	No	No	No
CYP3A4 Inhibitor	Yes	Yes	No	No	Yes
Excretion					
Total Clearance	0.564	0.605	0.204	-0.134	0.842
Renal Clearance	Yes	No	No	No	No
Toxicity					
Hepatotoxicity	Yes	No	No	No	No
Skin Sensitization	No	No	Yes	No	No

Metabolism data shows that all drugs, except for Remimazolam and Midazolam, do not inhibit CYP3A4. Remimazolam and Midazolam are CYP3A4 inhibitors, which can influence their interactions with other drugs metabolized by this enzyme. Propofol and Thiopental do not inhibit CYP3A4, potentially reducing the risk of drug-drug interactions. Remimazolam has a renal clearance profile, suggesting that it is excreted through the kidneys, while other drugs do not show this characteristic.

Toxicity profiling reveals that Remimazolam and Midazolam are not associated with hepatotoxicity or skin sensitization, making them safer options compared to Propofol, which does show potential for skin sensitization. Thiopental and Etomidate also exhibit favourable toxicity profiles with no significant hepatotoxicity or skin sensitization.

In summary, the docking scores, intermolecular interactions, and ADMET profiling collectively highlight Remimazolam as a promising anaesthetic with competitive binding affinity and a favourable

pharmacokinetic and toxicity profile. Midazolam also demonstrates strong efficacy and safety, while Propofol, Thiopental, and Etomidate show effective but comparatively weaker interactions and varying profiles in terms of ADMET characteristics.

Discussion

The molecular docking analysis and ADMET profiling present a comprehensive evaluation of the five intravenous anaesthetics, highlighting their binding affinities, intermolecular interactions, and pharmacokinetic properties about the $GABA_A$ receptor.

Midazolam emerged as the anaesthetic with the highest docking score (-7.1 kcal/mol), indicating its strong binding affinity and stable interaction with the $GABA_A$ receptor. This finding is consistent with Midazolam's clinical reputation as a highly effective sedative, commonly used for its rapid onset and significant efficacy. The intermolecular interactions further substantiate this, with key hydrogen bonds and halogen bonding providing enhanced stability. The ADMET profiling supports this with high human intestinal absorption (97.1%) and favourable CNS penetration, confirming its suitability for both oral and intravenous administration. However, its role as a CYP3A4 inhibitor necessitates careful consideration of potential drug-drug interactions, particularly in polypharmacy settings.

Remimazolam closely follows Midazolam, with a docking score of -6.9 kcal/mol. Despite the slightly lower score, Remimazolam's competitive binding affinity positions it as a strong alternative to Midazolam. The intermolecular interactions reveal a similar pattern of hydrogen bonds and hydrophobic contacts, which contribute to its effective receptor engagement. Its pharmacokinetic profile is particularly noteworthy; with a high human intestinal absorption (97.6%) and good CNS penetration, Remimazolam is well-suited for rapid induction and short-duration procedures. The renal clearance profile, in contrast to other anaesthetics, adds an advantage in terms of reduced hepatic burden, especially in patients with compromised liver function. The lack of hepatotoxicity and skin sensitization further enhances its safety profile, making it a promising candidate for wider clinical use.

Propofol and Etomidate exhibit moderate docking scores of -5.2 kcal/mol and -5.1 kcal/mol, respectively. These scores, while lower than those of Midazolam and Remimazolam, still reflect effective interaction with the $GABA_A$ receptor. Propofol's reliance on hydrophobic interactions, primarily with ILE130 and LEU128, indicates a more limited range of binding modes, which could explain its moderate efficacy. Nevertheless, Propofol remains a staple in anaesthetic practice due to its well-established pharmacokinetics and favourable ADMET profile, including high human intestinal absorption and non-inhibition of CYP3A4, which reduces the risk of drug-drug interactions. Etomidate's profile is similar, though slightly less robust, and its role in scenarios requiring stable hemodynamic conditions is well supported by its pharmacological properties. Both drugs lack the renal clearance feature seen with Remimazolam, but their non-inhibitory effect on CYP3A4 and absence of significant toxicity make them viable options in certain clinical contexts.

Thiopental had the lowest docking score (-4.7 kcal/mol), indicating the weakest interaction with the $GABA_A$ receptor among the five anaesthetics studied. Despite this, Thiopental's rapid induction properties have maintained its historical clinical use, particularly in settings where quick sedation is required. The intermolecular interactions, which include a mix of hydrogen bonds and hydrophobic contacts, are less diverse and robust, reflecting its lower docking score. Thiopental's ADMET profile shows acceptable

human intestinal absorption and no significant hepatotoxicity or skin sensitization, which supports its continued use, albeit in more specific scenarios where its rapid action outweighs its weaker receptor binding.

Limitations

This study, while providing valuable insights, has a few limitations that warrant consideration. The molecular docking analysis was performed in an in-silico environment, which, while informative, may not fully replicate the complexities of biological systems. Additionally, the receptor model used assumes a static conformation, which might not capture all possible binding interactions in a dynamic physiological setting. Although the ADMET predictions offer a useful overview of pharmacokinetic and safety profiles, these computational results would benefit from experimental validation to strengthen their clinical relevance. Lastly, while this study focused on the $GABA_A$ receptor, exploring interactions with other receptor subtypes could provide a more comprehensive understanding of the anaesthetic's effects. These considerations highlight areas for further research to build on the promising findings of this study.

Conclusion

This study underscores the significance of evaluating the binding affinities and pharmacokinetic properties of intravenous anaesthetics with the GABAa receptor, a pivotal target in the central nervous system for inducing sedation and general anaesthesia. Among the overall analysis of these anaesthetics, Remimazolam emerged as a highly promising agent. With a competitive docking score of -6.9 kcal/mol, Remimazolam demonstrates strong and stable interactions with key residues of the $GABA_A$ receptor, such as THR96 and GLN65, which are crucial for effective receptor engagement. Although Midazolam shows a slightly superior docking score of -7.1 kcal/mol, indicating stronger receptor binding, Remimazolam's pharmacokinetic profile offers significant clinical advantages, including rapid onset and short duration of action due to its metabolism by tissue esterase. Furthermore, Remimazolam presents a cleaner safety profile compared to other agents, notably showing no skin sensitization and reduced hepatotoxicity risks. While Propofol, Thiopental, and Etomidate exhibit weaker binding affinities and some safety concerns, Remimazolam's overall profile makes it a valuable and effective alternative, especially for outpatient settings and procedures requiring efficient anaesthetic management. This comprehensive analysis reinforces the potential of Remimazolam as a competitive and safer choice among intravenous anaesthetics, contributing valuable insights to its clinical application.

Conflict of Interest

There was no conflict of interest to declare.

Acknowledgement

We sincerely thank all individuals who contributed to this research.

References

[1]. Weir, C. J., Mitchell, S. J., Lambert, J. J., 2017, Role of GABAA receptor subtypes in the behavioural effects of intravenous general anaesthetics. *Br J Anaesth.* 119: i167–i175. Doi:10.1093/bja/aex369.

[2]. Ramasamy, K., Shanmugasundaram, J., Manoharan, R., Subramanian, V., Kathirvelu, P., Vijayaraghavan, R., 2022, Anti-neuropathic effect of 7,3′-dihydroxyflavone in paclitaxel induced peripheral neuropathy in mice involving GABAA, KATP channel and adenosine receptors. *Neurochem Int.* 159: 105388. Doi: 10.1016/j.neuint.2022.105388.

[3]. Marimuthu M., 2021, Dental impactions performed under general anaesthesia - A

retrospective study on the frequency and implications, *Int J Dent Oral Sci*. 1793–1796. Doi:10.19070/2377-8075-21000355.

[4]. Keerthika S, Mani G., 2021, Knowledge, attitude and practice of dentists towards dental procedures under general Anesthesia in children. *J Pharm Res Int.* 83–93. Doi:10.9734/jpri/2021/v33i20B31361.

[5]. Manivasagam D, Muthukrishnan A, Chaudary M., 2020, Assessment of effectiveness of local anesthesia with and without adrenaline in patients with cardiac disorders. *Int J Pharm Res.* 13. Doi:10.31838/ijpr/2021.13.01.217.

[6]. Dessai S, Ninave S, Bele A., 2024, The Rise of remimazolam: A Review of pharmacology, clinical efficacy, and safety profiles. *Cureus*. 16: e57260. Doi:10.7759/cureus.57260.

[7]. Kilpatrick G. J., 2021, Remimazolam: Non-Clinical and clinical profile of a new sedative/anesthetic agent. *Front Pharmacol*. 12: 690875. Doi:10.3389/fphar.2021.690875.

[8]. Noor N, Legendre R, Cloutet A, Chitneni A, Varrassi G, Kaye A. D., 2021, A comprehensive review of remimazolam for sedation. *Heal Psychol Res.;*9: 24514. Doi:10.52965/001c.24514.

[9]. Dao V-A, Schippers F, Stöhr T., 2022, Efficacy of remimazolam versus midazolam for procedural sedation: Post hoc integrated analyses of three phase 3 clinical trials. *Endosc Int open.* 10: E378–E385. Doi:10.1055/a-1743-1936.

[10]. Dong L, Sun T, Yang J, Zhou Y, Liu X, Liu Z, et al., 2024, Remimazolam has similar anesthetic effect and superior safety compared to propofol in elderly patients: A meta-analysis of randomized controlled trials. *World J Surg.* Doi:10.1002/wjs.12273.

[11]. Hoshino R, Ohashi N, Uta D, Ohashi M, Deguchi H, Baba H., 2024, Actions of remimazolam on inhibitory transmission of rat spinal dorsal horn neurons. *J Pharmacol Sci.* 155: 63–73. Doi: 10.1016/j.jphs.2024.04.002.

[12]. Masui K., 2024, Remimazolam: Its clinical pharmacology and evolving role in anesthesia and sedation practice. *Curr Opin Anaesthesiol.* 37: 344–351. Doi:10.1097/ACO.0000000000001384.

[13]. Kim, K. M., 2022, Remimazolam: Pharmacological characteristics and clinical applications in anesthesiology. *Anesth pain Med.* 17: 1–11. Doi:10.17085/apm.21115

[14]. Alharbi K. S, Almalki W. H, Alzarea S. I, Kazmi I, Al-Abbasi F. A, Afzal O, et al., 2024, Anaesthesia-induced changes in genomic expression leading to neurodegeneration. *CNS Neurol Disord - Drug Targets.* 23: 411–419. Doi:10.2174/1871527322666230508123558.

[15]. Mahmoud M, Mason KP., 2018, Recent advances in intravenous anesthesia and anesthetics. F1000Research. 7: 470. Doi:10.12688/f1000research.13357.1

[16]. Berman H. M, Battistuz T, Bhat T. N, Bluhm W. F, Bourne P. E, Burkhardt K, et al., 2002, The protein data bank. *Acta Crystallogr Sect D Biol Crystallogr.* 58: 899–907. Doi:10.1107/S0907444902003451.

[17]. Miller P. S, Aricescu A. R., 2014, Crystal structure of a human GABAA receptor. *Nature*.;512: 270–275. Doi:10.1038/nature13293.

[18]. Zielesny A., 2005, Chemistry software package chemoffice ultra 2005. *J Chem Inf Model.* 45: 1474–1477. Doi:10.1021/ci050273j.

[19]. Cousins K., 1993, ChemOffice Plus: A package of programs for chemists. *J Chem Inf Comput Sci.* 33: 788–789. Doi:10.1021/ci00015a603.

[20]. Morris G. M, Huey R, Lindstrom W, Sanner M. F, Belew R. K, Goodsell D. S, et al., 2010, AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J Comput Chem.* 30: 2785–2791. Doi: 10.1002/jcc.21256.AutoDock4

[21]. The PyMOL Molecular Graphics System, Version 2.0, Schrödinger, LLC. 2002. Available: https://pymol.org

[22]. SYSTÈMES D. BIOVIA Discovery Studio. Dassault Syst mes BIOVIA, Discovery Studio Modeling Environment, Release 2017.

Dassault Syst mes; 2016. Available: http://accelrys.com/products/collaborative-science/biovia-discovery-studio/

[23]. Pires D. E V., Blundell T. L, Ascher D. B., 2015, pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *J Med Chem.* 58: 4066–4072. Doi: 10.1021/acs.jmedchem.5b00104.

[24]. Jia C-Y, Li J-Y, Hao G-F, Yang G-F., 2020, A drug-likeness toolbox facilitates ADMET study in drug discovery. *Drug Discov Today*. 25: 248–258. Doi: 10.1016/j.drudis.2019.10.014.

[25]. Kesharwani R. K, Vishwakarma V. K, Keservani R. K, Singh P, Katiyar N, Tripathi S., 2020, Role of ADMET tools in current scenario: Application and limitations. *Computer-Aided Drug Design. Singapore: Springer* Singapore. pp. 71–87. Doi:10.1007/978-981-15-6815-2_4.