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# New drugs and anaesthesia

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The field of clinical anaesthesia has taken giant strides in terms of drug discovery and development. To date, the "ideal drug" does not exist—one with rapid onset of action, organ-independent metabolism, fast clearance, free from cardiorespiratory perturbations, minimal side effect profile. Recent drug innovations have focused primarily on matching previously unmet needs and identifying drawbacks of existing drugs and then altering their chemical structures to improve the safety and efficacy profile. There are currently numerous novel anaesthetic drugs at various stages of drug development.

**Keywords:** new drugs, anaesthesia, drug discovery, drug development

## Benzodiazepine

Midazolam is considered the gold standard as a potent sedative agent owing to its fast onset and its ability to offer amnesia. However, its active metabolite renders potent sedative potential, therefore lengthening its duration of action.

### *Remimazolam*

This new novel agent is the combination of two popularly used drugs, midazolam and remifentanil. This new water-soluble, ultra short-acting drug – which is classified as an intravenous benzodiazepine – has recently been approved by the Food and Drug Administration (FDA) for use in procedures requiring sedation in China and the USA, while South Korea and Japan have obtained approval for its use as a general anaesthetic agent.[1]

Remimazolam has been developed by structurally modifying midazolam, incorporating a carboxylic ester moiety into its benzodiazepine core. It has retained a similar pharmacological profile as midazolam, however, with an enhanced and improved pharmaco-chemical profile of rapid organ-independent hydrolysis into inactive metabolites. Its effects can be reversed with an antagonist at γ-aminobutyric acid type A ($GABA_A$) receptor, flumazenil.

As an agonist at $GABA_A$ receptors, it exerts its sedative effects by inhibiting neurotransmitter transmission from neural tissue. Evaluations from pharmacodynamic studies that were based on hypnotic depth indicators – such as bispectral index (BIS), Modified Observer's Assessment of Alertness/Sedation scores (MOAA/S) – revealed that, following a bolus dose, the time to onset and peak sedation was less than five minutes (min). The depth of sedation, as indicated by low BIS and MOAA/S scores, was equipotent. The mean recovery time described was between 5–20 min. Analysis from continuous infusion described even faster onset and offset times as well as a deeper level of sedation. Full recovery was reached within 20 min of infusion cessation.[2]

Several pharmacological analyses revealed that a single bolus dose of 0.01–0.30 mg/kg of remimazolam, when compared to 0.075 mg/kg of midazolam, exhibited a more rapid clearance (70.3 vs 23.0 L/h), a small steady-state volume of distribution (34.8 vs 81.8 L), a short elimination half-life (18 vs 102 min). Furthermore, after a three-hour constant rate infusion, the context-sensitive half-time of remimazolam and midazolam was 7.5 min and 40 min, respectively. The context-sensitive half-life (CSHT) is independent of the duration of infusion. It is highly protein-bound and excreted predominantly by the kidneys, unchanged.[2,3]

In comparison to propofol, remimazolam was found to have a similar pharmacokinetic profile: fast onset of action, recovery time, as well as the CSHT. Remimazolam displayed a non-inferior sedation efficacy. Assessment of the safety profile revealed that it had a lower rate of adverse events with regards to pain on injection, and cardiovascular and respiratory depression. With that said, it has gained favour as a hypnotic component of general anaesthesia in patients with lower American Society of Anesthesiology (ASA) physical status scores.

The pharmacokinetic properties remained unaltered along a diverse range of age groups, end-stage renal failure and moderate hepatic dysfunction. Pharmacological analysis was conducted on a small group of healthy volunteers; therefore, large-scale studies are required to fully elucidate the safety margins in these subgroups.[2]

Described adverse events of remimazolam include nausea and vomiting, headache, somnolence and occurrence of emergence delirium. Recommendations are made against the use of Ringer's lactate as a solvent. The solubility of remimazolam decreases in alkaline solution forming precipitates.[2]

Remimazolam is a safe alternative for intravenous sedation, and its place in clinical application has been widely supported by literature. Further clinical trials are required to assess the application and safety profile in paediatric and pregnant patients, as well as the development of a pharmacokinetic-pharmacodynamic (PK-PD) model for widespread application for target control infusion (TCI).

## Propofol derivative

Propofol, 2,6 disubstituted phenol derivative, has been an innovative, close-to-ideal anaesthetic agent with proven success in clinical application. However, its use is limited by undesired side effects, namely: haemodynamic instability and respiratory depression. Prolonged infusion poses a risk of propofol infusion syndrome (PIS) with resultant fatal metabolic derangements. The current formulation consists of an oil-in-water emulsion which carries setbacks such as pain on injection, bacterial contamination, emulsion emboli and hyperlipidaemia. Attempts at improving the side effect profile focused on developing an alternate emulsion formulation or non-emulsion-containing agents.

Over the years, a number of developed drugs have not enjoyed success in clinical practice.

### *Ampofol*

This agent contained a lower concentration of soybean oil and egg phosphatide, which supported less bacterial contamination but presented with a higher incidence of injection pain.[4]

### *Propofol-Lipuro*

Modified propofol with an increased proportion of medium-chain triglyceride (MCT) relative to long-chain triglyceride (LCT) saw the development of Propofol-Lipuro. The advantages it offered included a more rapid elimination of triglyceride and less pain on injection. This drug has not gained approval for its use yet. However, due to a related shortage of propofol drug product during the COVID-19 pandemic, the FDA issued an emergency use authorisation (EUA) permitting its use for continuous infusion, in patients 16 years and older.[5]

### *Ciprofol*

This novel agent, a 2,6-disubstituted alkylphenol, was initially designed to increase the steric effect on $GABA_A$ receptors therefore enhancing its inhibitory action on neural tissue and decreasing its lipophilicity. It has undergone Phase I and II trials in China and Australia and is currently registered in the USA as an anaesthetic induction agent.[6]

In comparable studies in healthy volunteers undergoing endoscopy procedures, as well as mechanically ventilated patients, ciprofol has equivalent anaesthetic efficacy, onset, recovery, and clearance rate after infusion, to that of propofol. It paraded better tolerability, with improved cardiovascular stability. The main advantage reported was a reduced incidence of pain at injection site. The present body of works have not reported an incidence of PIS, however, more comparative studies with a larger sample size are required to establish its superiority or comparability to propofol.[6,7]

### *Fospropofol disodium*

Since its approval by the FDA as a sedative-hypnotic agent (2008), fospropofol has gained acceptance over propofol for procedures requiring monitored anaesthetic care. In an attempt to resolve the setbacks associated with the lipid emulsion, a prodrug was developed to increase the miscibility of propofol. A prodrug undergoes hydrolysis by tissue phosphatases releasing active compounds: propofol and formaldehyde.

This sedative-hypnotic agent has recently been discontinued due to slower onset of effect, longer recovery times as well as its propensity to elicit perineal pain and pruritis.[8]

## Neuro-steroid

### *Phaxan*

Alfaxalone (Althesin) is a water-insoluble, neuroactive steroid, formulated in CremaphorEL. This established intravenous hypnotic was withdrawn from clinical practice because of hypersensitivity experienced to the CremaphorEL. Phaxan is reformulated Alfaxalone in 7-sulphobutylether beta-cyclodextrin, enabling drug dispersion in water. A Phase 1 human trial that compared it to an equipotent propofol dose showed that Phaxan displayed fast-onset, short-duration anaesthesia with rapid cognitive recovery similar to propofol. There was less cardiovascular depression and no obstruction to the airway. No pain on injection was observed.[9]

## Etomidate analogues

Etomidate is distinct from other popularly used hypnotic agents by retaining a stable cardiorespiratory profile. However, etomidate suppresses the adrenocortical axis by the inhibition of the enzyme 11β-hydroxylase, making it unsuitable for administration by prolonged infusion. Therefore, intravenous infusions limited its administration to critically ill patients. Prior to administration, due consideration and patient selection, in whom the benefit of haemodynamic stability outweighs adrenocortical suppression, needs to be exercised.

The first etomidate analogue to be discovered in studies conducted in rats, was methoxycarbonyl-etomidate (MOC-etomidate). This drug underwent ultra-rapid metabolism by non-specific esterases to form a carboxylic acid. This inactive metabolite showed a low affinity to the hydrophobic catalytic site on the 11β-hydroxylase enzyme, therefore, did not produce adrenocortical suppression. The fast pharmacokinetic properties of MOC-etomidate implied that large drug concentrations were required to maintain an acceptable depth of anaesthesia in rats. The unintended results were adrenocortical suppression and delayed recovery times. Subsequent modifications of the MOC-

etomidate core structure resulted in the protection of the ester moiety, therefore reducing the rate of hydrolysis.[10]

### *ABP-700*

ABP-700 (Cyclopropyl-methoxycarbonyl metomidate) is a second-generation analogue. A Phase 1 randomised control trial conducted on healthy volunteers to assess safety, tolerability, and clinical effect of continuous infusion of ABP-700, showed promising pharmacodynamic and pharmacokinetic profiles. No serious adverse events were reported. Haemodynamic and respiratory effects included mild dose-dependent tachycardia, slightly elevated blood pressure but no centrally mediated apnoea. Adrenocortical depression was not observed. An important drawback reported was dose-dependent involuntary muscle movements. The aetiology of these movements is unknown and warrants further research.[3,10,11]

## New PK-PD models

TCI systems are well-validated and clinically available as a mode of intravenous drug administration. Computerised infusion pumps with incorporated PK-PD software, titrate drugs towards a user-defined drug concentration at specific target sites. Since the approval of the first generation delivery system designed for just propofol (1996), the subsequent generations broadened the drug scope to include remifentanil, alfentanil, sufentanil and their respective models, allowing for more user options.[11]

Published TCI models were developed using data from narrow demographic variability. Patients with altered physiology to the lean adult population, such as the paediatric, elderly and obese population, were not included. Kataria and Paedfusor propofol models have been developed specifically for use in paediatric patients. A single agent with multiple PK-PD models poses a potential risk of inappropriate model selection for a patient type, therefore limiting its use by users.

Innovations in technology and databases collected universally have brought about the generation of new "general purpose" PK-PD model.

### *Eleveld PK-PD model*

This innovative general-purpose TCI model is designed to be more inclusive of a wider population range with improved coordination between patients' clinical status and the selected model.[12]

The Varvel criteria are used to determine the performance of TCI models. Drug concentration levels at a point in time are compared to those predicted by a model to determine the median performance error (MdPE), median absolute performance error (MdAPE) to assess bias and precision respectively. MdPE value below 20% and a MdAPE of less than 40% are considered clinically acceptable levels.[11,13]

The Eleveld propofol model has been shown to have a low bias and low precision for the paediatric, elderly and obese population. The performance profile in obese patients showed an MdPE of less than 2% and MdAPE of less than 10%. The compelling high-performance evidence of the general purpose model compared to other PK-PD models is a suitable alternative to commercially available TCI models.

The Minto remifentanil model is based on a dataset collected on 65 lean adults. Merging data collected from several studies along with a newly developed general-purpose model, a more broadly applicable PK-PD model that can be clinically applicable in children and obese patients can be seen.

## Conclusion

With increasing life expectancy and growing populations, there is a growing demand for healthcare systems to meet patients' needs and to reduce the burden of disease. These innovative drugs and drug delivery systems have shown promising results, which, in turn, means new treatment options for patients and advances in health care.

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