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REVIEW

There is no context for this sensitive matter – mixing of propofol and remifentanil for total intravenous anaesthesia

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Total intravenous anaesthesia (TIVA) is increasingly employed in anaesthetic practice due to its specific benefits in certain patient populations. TIVA for general anaesthesia typically necessitates using at least two syringe pumps – one for each agent, propofol and remifentanil. Resource limitations have led to the practice of mixing these agents in a single syringe, subsequently infused using a propofol-based model. This approach is problematic due to significant concerns regarding the chemical and physical incompatibility of the drugs. Evidence demonstrates that this mixture of propofol and remifentanil is chemically and physically unstable. This is due to the pH-induced degradation of remifentanil, which reduces its concentration and therapeutic efficacy. Additionally, propofol emulsions become physically unstable, resulting in aggregation and increased percentage of fat residing in globules larger than 5 µm (PFAT5) values. Pharmacokinetic and pharmacodynamic considerations further highlight the impracticality of mixing these agents, as maintaining mixture homogeneity and consistent drug levels is challenging and raises safety concerns. Consequently, formal guidelines from the South African Society of Anaesthetists (SASA) and the Medical Protection Society (MPS) advise against this practice. This review summarises the current evidence to confirm that mixing propofol and remifentanil is unsafe and should be avoided in clinical practice.

Keywords: total intravenous anaesthesia, target-controlled infusion, drug interactions

Total intravenous anaesthesia and the practice of mixing propofol and remifentanil

TIVA is an anaesthetic technique gaining popularity for its numerous clinical benefits and lower environmental impact. The Association of Anaesthetists recommends using TIVA instead of volatile agents to reduce the environmental impact of anaesthesia.[1] TIVA involves administering intravenous anaesthetic agents to achieve certain anaesthetic goals, namely sedation with or without analgesia. Its greatest clinical benefits are in patients at risk of malignant hyperthermia and patients with a history of severe postoperative nausea and vomiting, myasthenia gravis, or a neuromuscular disorder where neuromuscular blockers are contraindicated. TIVA is also preferred in "tubeless" ear, nose, and throat and thoracic surgeries, procedures requiring electrophysiological monitoring, anaesthesia outside the operating room, and transferring anaesthetised patients.[2]

While TIVA can be performed with a single agent, such as ketamine for sedation or propofol for endoscopy, general anaesthesia typically uses a regimen of propofol and remifentanil administered in separate syringes. An emerging trend in South Africa and internationally is for clinicians to mix propofol and remifentanil in a single syringe due to a lack of multiple infusion pumps. This practice raises questions about the safety and efficacy of mixing these drugs for TIVA.

This article aims to critically examine the practice of mixing propofol and remifentanil for TIVA, evaluate the potential risks and benefits, and highlight why this practice should be avoided.

Background

In December 2022, SASA advised against administering, prescribing, or mixing medications outside the specifications provided by the manufacturer or package insert, as stated in their 2022 guidelines.[3] These guidelines emphasise strict adherence to best practices when handling lipid emulsions (such as propofol), cautioning that mixing them with other medications can cause significant alterations in drug stability, pharmacokinetics, and pharmacodynamics, potentially affecting the stability of the mixture and its efficacy. Dr. Graham Howarth, Head of the MPS, also authored an editorial emphasising the risks of drug mixing and off-label medication use.[4]

Rationale for mixing propofol and remifentanil

The primary rationale for mixing propofol and remifentanil in a single syringe is often driven by resource constraints, such as the limited availability of target-controlled infusion (TCI) and syringe pumps. This issue affects adult and paediatric anaesthesia globally. In adult anaesthesia, mixing these agents becomes a practical necessity due to the lack of pumps.[5,6] In paediatric anaesthesia, particularly in countries like the United Kingdom (UK) and Canada, the decision to mix these drugs is motivated by the need for speed and simplicity during short-duration procedures.

A study by Bagshaw et al.,[7] which observed paediatric anaesthetic practices in the UK, cited an article (analysing 291 responses) indicating that 24% of respondents in the UK and Ireland frequently or consistently used mixtures, with another 14% using them occasionally. The study, which collected data on 880 patients (with 873 included in the final analysis due to seven

incomplete records), is often cited as evidence of the safety of this mixture, as no serious side effects were observed.[7] However, it is important to note that the study was purely observational. Proponents claim that the approach of mixing these two drugs allows for faster patient turnover, reduces material waste, and simplifies drug administration, especially for practitioners less experienced in TIVA.[8,9] Additionally, simultaneous down-titration during recovery may facilitate faster emergence from anaesthesia, enhancing operational efficiency.

Importance of drug stability

Propofol is a highly lipid-soluble phenolic derivative that is insoluble in water and must be formulated as a lipid-in-water emulsion. The pH of propofol, in its emulsion form, is typically between 6.0 and 8.5. Emulsion stability relies on maintaining the repulsive forces between lipid droplets, known as the zeta potential. Factors such as pH and the presence of electrolytes (sodium, potassium, calcium, magnesium, and iron) can destabilise the emulsion by neutralising the negative charges on droplet surfaces, potentially leading to hydrolysis of the emulsifier. A decrease in the zeta potential may initiate destabilisation processes like flocculation, coalescence, creaming, and cracking, causing lipid molecules to form larger droplets. This degradation affects the release and distribution of propofol in vivo, altering its pharmacokinetics. For example, decreased droplet surface area can lead to inconsistent drug delivery and an increased risk of emboli due to enlarged oil droplets.[10] Remifentanil (the pH of reconstituted remifentanil is typically between 2.5 and 3.5) is also sensitive to pH changes, with a rise in pH causing its ester linkage to break down, impacting drug stability and availability.[11] These chemical interactions can significantly affect these drugs' pharmacokinetics and precise dosing, impacting therapeutic efficacy and patient safety.

Examining the stability of propofol and remifentanil mixtures

"Mixing" refers to combining different anaesthetic drugs in the same syringe for administration to a single patient. The primary concerns are the chemical and physical stability of the mixture and potential pharmacokinetic and pharmacodynamic interactions. Chemical stability is assessed using high-performance liquid chromatography to determine drug concentrations and identify degradation products. Physical stability involves assessing miscibility, monitoring pH, and inspecting for precipitation, all of which could indicate issues with drug solubility, potentially leading to instability and reduced efficacy. Instability in the mixture can reduce active drug concentration, leading to suboptimal dosing and poor therapeutic outcomes.

Mixing can alter drug potency, potentially causing unintended potentiation or attenuation of effects, and may increase the risk of adverse effects due to synergistic or additive interactions. Understanding the pharmacological properties of each drug and the appropriate concentration ratios is crucial to maintaining therapeutic effectiveness and minimising risks.

Numerous studies have investigated the stability of propofol and remifentanil mixtures, with most demonstrating instability. Stewart et al.[12] found that remifentanil concentrations decreased significantly when mixed with 1% propofol due to the alkaline pH of propofol causing degradation. O'Connor et al.[13] studied the homogeneity and stability of propofol-remifentanil admixtures in polypropylene syringes. They tested mixtures of 1% propofol with remifentanil concentrations of 25, 50, and 100 µg/ml. Syringes were placed vertically, and drug concentrations were measured at the top and bottom over 300 minutes. The study found significant separation, with remifentanil consistently concentrated at the top and propofol at the bottom, most notably in the 25 µg/ml mixture. For example, at 10 minutes, remifentanil was 16 µg/ml at the top and 4 µg/ml at the bottom, while propofol was 5.3 mg/ml at the top and 8.6 mg/ml at the bottom. Additionally, drug concentrations were often below 90% of the expected values, indicating chemical instability. The 100 µg/ml mixture showed better stability for remifentanil, but propofol was still separated. The study faced criticism for using higher-than-typical remifentanil concentrations and the static, vertical syringe positioning, which does not accurately reflect standard TIVA conditions. The authors noted that a horizontal syringe orientation during infusion might improve mixing.

In response to O'Connor's findings, Wylie et al.[14] conducted a study to assess the chemical stability of remifentanil mixed with 1% propofol at a concentration of 5 µg/ml, tailored for paediatric use. Samples were collected at several intervals over 57 minutes, reflecting the median surgery time reported in a previous study of over 1.5 million paediatric cases. The study found that remifentanil remained stable within a clinically acceptable range, consistently maintaining a concentration of 5 ± 0.5 µg/ml, regardless of infusion duration or simulated patient weight. However, the stability of propofol in the mixture was not addressed.

Nemec et al.[6] investigated the physical stability of propofol emulsions when mixed with high concentrations of remifentanil. They tested 1% and 2% propofol emulsions combined with remifentanil at 50 µg/ml and 100 µg/ml, using microscopy to assess the formation of aggregates. The study found that aggregates formed immediately after mixing remifentanil with both 1% and 2% propofol emulsions.

Gersonde et al.[15] conducted a study assessing propofol's physical and chemical stability when mixed with nine sedative and analgesic drugs, focusing on the stability of a propofol-remifentanil combination over seven days. They evaluated three mixing ratios (10:1, 1:1, and 1:10), deeming the entire mixture incompatible if any ratio was unstable. The 10:1 ratio (10 ml of 1% propofol and 1 ml of 50 µg/ml remifentanil) showed significant instability. The remifentanil concentration fell from slightly above 90% at one hour to 74.4% at four hours, 30.4% at 24 hours, and became undetectable after four days. This instability was linked to pH-dependent degradation, with higher pH levels accelerating remifentanil hydrolysis. Physical stability was also poor, with several physical parameters deviating from expected,

indicating emulsion instability. Visually, the mixture changed colour from white to light yellow within 24 hours. Overall, the study concluded that the propofol-remifentanil mixture is neither chemically nor physically stable due to the pH-related remifentanil degradation and propofol emulsion destabilisation.

Nilsson et al.[16] assessed the physical stability of three propofol emulsions (Propolipid®, Propofol-®Lipuro, and Diprivan®) when mixed with remifentanil in various ratios, focusing on parameters like pH, mean droplet diameter (MDD), polydispersity index (PDI), and PFAT5. They tested four ratios (remifentanil to propofol): 10:1, 20:1, 1:1, and 1:20, using both 1% and 2% propofol to simulate intensive care unit conditions. For 1% propofol (10 mg/ml), PFAT5 exceeded the recommended 0.05 limit after four hours, indicating instability. With 2% propofol (20 mg/ml), PFAT5 values were elevated immediately, signalling rapid destabilisation. Key findings were that higher propofol concentrations, longer mixing durations, and lower pH (from higher remifentanil concentrations) all increased PFAT5. The 1:20 ratio (excess propofol) showed better stability with PFAT5 below the threshold. Although MDD, PDI, and zeta potential remained within normal ranges, PFAT5 was the key indicator of instability, especially in higher remifentanil ratios and prolonged infusions. The study highlights the risks of prolonged infusion and high propofol concentrations, with PFAT5 values exceeding safe limits, potentially compromising infusion safety.

Henkel et al.[11] studied the stability of remifentanil and propofol mixtures, focusing on pH levels, reconstitution media, and drug concentrations over 24 hours. They reconstituted remifentanil at concentrations of 10, 20, 30, 40, and 50 µg/ml using various media: water, 0.9% saline, 20% saline, and sodium bicarbonate. The latter two were chosen to test extreme pH conditions. Remifentanil alone maintained over 92% of its expected concentration in water, 0.9% saline, and 20% saline, where the pH was between 3.74 and 3.95, indicating stability in these acidic conditions. However, when mixed with propofol, remifentanil degraded significantly across all diluents, with 50–60% concentration reductions after 24 hours. This suggests that the interaction with propofol significantly contributes to remifentanil's degradation. Sodium bicarbonate, with a higher pH of 8.65, caused rapid remifentanil degradation, resulting in undetectable levels after 24 hours, with major degradation occurring within one hour. Propofol remained chemically stable, retaining over 97% of its concentration after 24 hours and showing no signs of emulsion instability across different diluents. The study found that mixing remifentanil with propofol increased the solution's pH, moving closer to the range where remifentanil undergoes rapid hydrolysis. For example, remifentanil in 0.9% saline increased pH from 3.94 to 6.86 when mixed with propofol. This pH shift contributes to remifentanil's degradation, highlighting the critical role of pH in maintaining its stability.

These studies show that mixing remifentanil and propofol causes chemical and physical instability, leading to potential therapeutic inefficacy. Remifentanil degrades with increased pH, while propofol exhibits physical instability through changes in globule size and zeta potential. These results highlight the risks and strongly advise against their combined use.

Pharmacokinetic and pharmacodynamic rationale for not mixing propofol and remifentanil

During TIVA guided by TCI, propofol and remifentanil are typically administered separately using specific pharmacokinetic models to achieve precise drug delivery. Propofol is typically administered using the Schneider, Marsh or Eleveld models, while remifentanil uses the Minto or Eleveld models.[17-23] This separation allows for a synergistic interaction between these drugs, enabling dose reductions and improving therapeutic effects.[24]

Mixing propofol and remifentanil raises concerns due to their differing pharmacokinetic properties. Propofol will accumulate in peripheral compartments as the operation proceeds, requiring a gradual reduction in infusion rate during surgery to prevent overdose. This reduction is managed by propofol's pharmacokinetic models, which adjust the rate to maintain the desired concentration.[25] In contrast, remifentanil does not accumulate because of its rapid metabolism, so any decrease in its infusion rate can quickly lead to underdosing and inadequate analgesia.[26] Mixing these drugs and infusing them using a propofol model could lead to a decrease in remifentanil doses, leading to poor pain management.

Additionally, using fixed concentrations of remifentanil, such as 50 µg/ml, increases the risk of side effects like bradycardia, hypotension, and apnoea, especially when both drugs are given in bolus together. Conversely, a 5 µg/ml concentration might be insufficient for effective analgesia, particularly with a reduced propofol dose. This concentration is often used in paediatric anaesthesia, where sedation is the primary goal. Here, a low concentration may provide excessive sedation and apnoea risk without significant analgesia.[27]

Another issue is the chemical and physical instability between propofol and remifentanil, which complicates the determination of the exact dosage of each drug administered when mixed. TCI aims to deliver precise amounts of each drug, but mixing the drugs increases uncertainty about dosage, risking inadequate analgesia, over-sedation, or insufficient anaesthesia depth.

Moreover, mixing these drugs prevents independent titration of each drug to its desired effect. Adjusting sedation should involve altering propofol alone, while analgesia should be controlled by adjusting remifentanil independently. Mixing creates a fixed-dose infusion, limiting the ability to adjust dosages to meet the patient's needs and potentially leading to adverse outcomes.

In 2018, following the 5th National Audit Project audit, the journal *Anaesthesia* published a guideline from the Association of Anaesthetists and the Society for Intravenous Anaesthesia on the safe practice of TIVA.[28] The guideline highlights previously mentioned concerns regarding pharmacokinetic and pharmacodynamic limitations, particularly the inability to titrate each drug independently, a key factor in controlling

both the depth of anaesthesia and analgesia. Also, as discussed, mixing can result in phase separation and chemical instability, potentially compromising drug efficacy and leading to inconsistent dosing. The guideline further emphasises the risk of excessive remifentanil boluses during rapid propofol delivery in TCI systems, which could result in haemodynamic instability and respiratory depression.

Legal considerations

As previously stated, SASA and MPS advise against mixing drugs. Although not illegal, this practice deviates from standard care and requires significant justification. Any deviation from standard practice must withstand scrutiny by the Health Professions Council of South Africa, which requires that clinical practices be defensible and justifiable in case of complaints or inquiries.

Conclusion

Mixing propofol and remifentanil is occasionally done due to resource constraints, but this practice presents significant risks that outweigh any potential benefits. Evidence consistently shows that the mixture is chemically and physically unstable. Remifentanil rapidly degrades in the presence of propofol due to pH changes, resulting in reduced concentrations and therapeutic efficacy. Additionally, propofol emulsions become physically unstable, leading to aggregation and increased PFAT5 values. From a pharmacokinetic and pharmacodynamic perspective, there is scant justification for this practice, and maintaining homogeneity and consistent drug levels is challenging, posing further safety concerns. Given these issues, it is strongly recommended that propofol and remifentanil be administered separately to ensure their stability and effectiveness, comply with numerous safety guidelines, and reduce the risk of complications.

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Conflict of interest

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