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Pharmacokinetic–Pharmacodynamic Correlation of Sedatives and Analgesics in Critical Care Settings: A Quantitative Bioanalytical Study

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Abstract

The components of intensive care management could not live without sedation and analgesia, but the optimal pharmacological balance of patients who are in critical care is still complex because of physiological variability and drug metabolism modifications. This research involves the pharmacokinetic pharmacodynamic (PKPD) interactions between midazolam, fentanyl and propofol in order to determine quantitative relations between plasma concentrations and clinical outcomes. A case of a prospective observational study was aimed at 100 patients in the ICU who were given midazolam (n=34), fentanyl (n=33) or propofol (n=33) continuous infusions. Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to analyse serum plasma samples and was followed with FDA bioanalytical standards (bias older 5 per cent, CV decreased 7 per cent). At the same time, the appraisal of sedation and analgesia was evaluated by means of the Richmond Agitation sedation Scale (RASS) and Critical-Care Pain Observation Tool (CPOT). Non-compartmental and Spearman rank were used to statistically analyse pharmacokinetic and PKPD correlations. The three agents all had concentration-dependent pharmacodynamic effects with significant negative relationships between plasma concentrations and RASS/CPOT scores (midazolam ϱ = -0.88; fentanyl rho = -0.79; propofol rho = -0.74; p< 0.001). Under constant infusion, predictable pharmacokinetic behavior was observed, with steady-state concentrations being attained in 1216hours. Quantitative PK -PD relationships using LC-MS/MS confirm that plasma drug concentration is a strong predictor of sedation and the depth of analgesia. The results indicate the accuracy of dosing and tailored sedation regimens in the critical care unit to reconcile bioanalytical exactness with clinical pharmacology towards optimum healing results.

Keywords: Pharmacokinetics; Pharmacodynamics; Sedation; LC–MS/MS; Critical care bioanalysis

1. Introduction

Patients with critical illnesses are usually in need of constant sedation and analgesia to assist in mechanical ventilation, agitation avoidance, and physiological stability in intensive care units (ICUs). But there is still a gap between the ideal sedation and the most difficult part of critical care pharmacotherapy since the differences in the disposition and response of the drug are so vast, causing interindividual differences. The correlation of pharmacodynamics and pharmacokinetics of sedatives and analgesics offers a critical platform through which the clinical effects of plasma levels on depth of sedation and analgesia levels (Franken et al., 2018). With the development of intensive care medicine in the direction of personalized pharmacology, the need to measure this relationship with the help of solid bioanalytical methodologies has

become an essential part of the exact dose and the optimization of safety.

The most common agents used in the practice of sedation and analgesia of critically ill adults include midazolam, fentanyl, and propofol (Gomers et al., 2008). Midazolam is a benzodiazepine with a short-acting period, the action of which occurs by modulating the icycloheptane (GABA) receptor, causing anxiolysis, amnesia and sedation. Fentanyl is a strong synthetic opioid that binds mostly to μ-opioid receptors, which offers quick onset short-acting analgesia and sedation since it is highly lipid soluble. Propofol is a phenolic intravenous anesthetic that causes GABAergic inhibition and dose-dependent hypnosis (Trapani et al., 2021). Although largely utilized, it is the pharmacokinetic variability because of altered hepatic metabolism, renal dysfunction and extracorporeal treatments that usually complicate drug titration in the ICU setting (Roberts et al., 2013). In turn, the combination of PK and PD information using plasma concentration levels with pharmacodynamic (PD) scoring systems, including the Richmond Agitation Sedation Scale (RASS) and the Critical-Care Pain Observation Tool (CPOT), becomes essential to maximize treatment and reduce the negative impacts.

Dynamic physiology of the critical illness is a major factor that affects drug pharmacokinetics, which is mainly affected by alteration in plasma protein binding, tissue perfusion, and organ clearance (Hanks et al., 2022). As an example, midazolam is hepatically metabolized by CYP3A4, however, the clearance of the drug is significantly decreased in patients with multiple organ dysfunctions or concomitant use of enzyme inhibitors (Wang et al., 2016). Equally, distribution and elimination of fentanyl changes when exposed to extra-corporeal membrane oxygenation (ECMO) or renal replacement therapy (RRT) (Ha et al., 2017). Obesity, age, and lipid solubility affect the propofol drug pharmacokinetics, leading to complex nonlinear accumulation (Morse et al., 2023). Therefore, the clinical decision-making on the individualized sedation regimen is informed by the knowledge of these variations in bioanalytical quantification and PK-PD modelling.

The development of superior liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods has made it possible to measure low-concentration analytes in complicated biological samples accurately, thus providing the feasibility of the plasma drug concentration determination (veringa et al., 2016). This level of rigor of the analytical studies provides the basis of bioanalytical studies, intended to correlate pharmacodynamic endpoints with pharmacokinetic parameters. Correlation analysis of plasma concentration and RASS or CPOT scores in clinical pharmacology gives an empirical relationship between drug exposure and clinical response which can be used to regulate dosing (Griffin et al., 2020). Using proven LC-MS/MS assays and standardized PD instruments, scientists will be able to explain quantitative associations that drive titration to optimum therapeutic ranges and reduce adverse outcomes like oversedation, hypotension or delayed emergence.

The need to incorporate PK-PD models in ICU sedatives and analgesics has been underscored by recent research in order to attain specificity in therapy. According to Vandemoortele et al. (2022), target-controlled infusion (TCI) systems, which relies on PK-PD models, can reduce the variability of sedation depth as opposed to manual titration; the authors also found that the system enhanced patient outcomes and ventilation time.Tosca et al. (2024) also demonstrated that continuous pharmacokinetic monitoring of the patient led to reduced variability in sedation depth, which is improved under the influence of the target controlled infusion (TCI) system. In spite of these developments, lack of comparative PK-PD correlation with simultaneous midazolam, fentanyl, and propofol under the constant infusion settings in critically ill groups is still evident. Majority of the past studies have only examined these agents individually or in non-critically ill groups and this does not allude to the extent to which they can be generalized to the ICU environment.

Considering the complications of changed physiology in acute disease, quantitative evaluation of PK–PD connections provide the way to precision medicine in sedation management. The knowledge of interactions between plasma drug concentrations and sedation or pain scores enables clinicians to more accurately predict clinical response and develop evidence-based strategies to use with the infusion (Kissin et al., 2021). In addition, the determination of concentration levels that are linked to therapeutic effectiveness or toxicity can be used in establishing optimal dosing levels. Model-informed precision dosing (MIPD) strategies, which are based on PKPD modelling and real-time analytics, have a future in promoting drug efficacy and safety in intensive care (Chawla et al., 2022).

This gap is aimed to be covered by the current bioanalytical research that will quantitatively measure the correlation between plasma concentrations of midazolam, fentanyl, and propofol and their respective pharmacodynamics in a heterogeneous population in a ICU. The aim of the study is to determine quantitative relationships between RASS and CPOT scores, which can be used to tailor the process of sedation and analgesia procedures to each patient through the use of validated LC–MS/MS analysis and the simultaneous measurement of the two variables. In this way, it is part of the greater aim to combine bioanalytical science with clinical

pharmacology to maximize therapeutic interventions of highly ill patients. Moreover, the results will contribute to the improvement of the knowledge of interindividual variability, sustain PKPD modelling models, and introduce the base of subsequent research that will involve machine learning algorithms and adaptive infusion systems. Finally, this study complies with the concept of translational pharmacology in which stringent bioanalytical quantification is combined with clinical decision-making in the bedside to enhance the outcome of critical care pharmacotherapy.

2. Methodology

In this study, a prospective observational pharmacokinetic-pharmacodynamic (PK-PD) design was utilized to assess quantitative relationship between plasma concentrations of midazolam, fentanyl and propofol with their respective sedative and analgesic effects in patients who are in critical care. This study was carried out in agreement with the ethical principles of the declaration of Helsinki and it was approved by an institutional review board of the tertiary care hospital involved. All the patients were informed and signed a written informed consent or their legal representatives before being included in the study.

2.1 Study Design and Patient Population

One hundred and ten adult patients admitted in intensive care unit (ICU) needing constant sedation and analgesics were recruited. These inclusion criteria included: (1) patients aged between 18 and 80 years, (2) the use of mechanical ventilation over a period of more than 24 hours, (3) the use of one of the study drugs (midazolam, fentanyl or propofol) by continuous intravenous infusion and (4) hemodynamic stability at the time of sampling. The exclusion criteria were severe hepatic failure (ALT/AST more than 5 times above the upper limit), a pregnancy or exposure to neuromuscular blockers within the past three months, or hypersensitivity to the study drugs.

Those patients put in the enrolled condition were thirty-four on midazolam, thirty-three on fentanyl, and thirty-three on the propofol infusions. Demographic and clinical characteristics (age, sex, weight, sequential organ failure assessment (SOFA), creatinine clearance, extracorporeal membrane oxygenation (ECMO) or renal replacement therapy (RRT) were taken at the baseline (mean age = 62.02 SD = 12 years; mean weight = 75.02 SD =12 kg; mean SOFA = 9.03 SD = 3). These properties guaranteed the presence of a heterogeneous and clinically representative ICU cohort.

2.2 Drug Administration Protocol

Patients were treated based on the institutional ICU sedation protocol. The following were the sedative analgesic regimens: Midazolam was given with an initial rate of 0.021mg/kg/h which was adjusted to a target Richmond Agitation Sedation Scale (RASS) of -3, -5. Fentanyl was given at the rate of 1-3 ug/kg/h to obtain perfect analgesia (Critical-Care Pain Observation Tool [CPOT] ≤2). Propofol infusion was set at 1-3mg/kg/h and adjusted to ensure deep sedation with a minimum of hemodynamic impairment. Volumetric infusion pumps were used to execute all the infusions through specific lines. Titration was done by attending intensivists who were blinded to the continued PK analysis to ensure clinical assessment was unbiased. The comorbid drugs like vasopressors and antibiotics were also noted down to measure the possible pharmacokinetic interaction.

2.3 Sampling and Bioanalytical Procedure

The venous tissue samples were taken at eight predetermined time points (0.5, 1, 2.4, 4, 8, 12, 16 and 24 hours) following the beginning of the infusion. The samples (5 mL each) were poured into heparinized tubes and centrifuged at 3,000 rpm and 10 min before storing the plasma aliquots at -80 C.

The quantification of the drugs was done based on a validated liquid chromatography-tandem mass spectrometry (LCMS/MS) assay. The separation was carried out through chromatography using a C18 column (2.1 x 100 mm, 3 u m) in a gradient elution with a mobile phase of acetonitrile and 0.1% formic acid in water. The detection was performed on a triple quadrupole mass spectrometer which was used in positive electrospray ionization mode. The midazolam (10 200 ng/mL), fentanyl (0.1-5.0 ng/mL) and propofol (500-4000 ng/mL) calibration curves were built. Analytical validation was in accordance with the U.S FDA bioanalytical method validation requirements. The assay reliability was assessed by ensuring that the intra- and inter-assay accuracy (bias) was within a range of -5% and precision (coefficient of variation, CV%) was not greater than 7% at all levels of QC. There were no noticeable matrix effects or carry over.

2.4 Pharmacodynamic Assessment

The pharmacodynamic endpoints were also compared alongside the PK sampling with standardized clinical tools:

a) Sedation severity was measured by means of the Richmond Agitation-Sedation Scale (RASS), a scale with +4 (combative) to -5 (unarousable).

b) Analgesia was measured by the Critical-Care Pain Observation Tool (CPOT) and the scale was between 0 (no pain) to 8 (severe pain). Trained ICU nurses, who were blinded to the data on plasma concentrations, were used in recording the scores to

create objectivity. The aiming range of sedation was RASS -3 to -5 and acceptable analgesia was CPOT of 2. Improved PD quantification These standardized measures allowed strong correlation analysis of PD.

2.5 Pharmacokinetic and Pharmacodynamic Analysis

Plasma concentration-time curve was plotted on each drug to see the steady-state attainment and variability. The non-compartmental analysis was used to calculate descriptive pharmacokinetic parameters, such as steady-state concentration (Css), time to steady-state (Tss) and coefficient of variation.

To be able to compute pharmacodynamic modelling, Spearman rank correlation coefficients (0) were calculated to determine the strength and direction of relationships among plasma drug concentrations and PD measures (RASS and CPOT). There were significant negative correlations, which showed that deepening of sedation and pain relief was predictable with increasing plasma concentrations (midazolam ϱ = -0.88; fentanyl rho = -0.79; propofol rho = -0.74; all p = 0.001).

Continuous variables were represented in mean SD. One-way ANOVA was used to compare the years between drugs and then post hoc with Bonferroni correction. A p-value of less than 0.05 was taken as a significant one.

2.6 Quality Control and Data Integrity

2.7 Ethical Considerations and Safety Monitoring

The quality analytical procedure was within the requirements of Good Laboratory Practice (GLP). Each batch contained quality control samples at low, medium and high concentration levels. The inter-day variability was minimized through internal standard calibration. The integrity of data was confirmed by the method of double-entry validation and cross-checking of analytical and clinical data.

The institutional ethics committee approved all the study procedures. Unfavourable occurrences involving sedation or drug infusion like hypotension, bradycardia, respiratory depression were recorded and were treated according to the ICU guidelines. The confidentiality of the patients was ensured by anonymizing the data by coding the code and limited access to distinguishable data.

3. Results

One hundred critically ill patients were enrolled in the study with thirty four on midazolam, thirty-three on fentanyl and thirty-three on propofol as continuous infusion to gain sedation and analgesia. These patients were a common representative of intensive-care population that has different levels of organ dysfunction. Table 1 includes the demographic and baseline clinical characteristics. The average (SD) age was 62.112 years, and the average body weight was 75.112 kg. The SOFA score of 9 ± 3 and the mean creatinine clearance was 75 ± 25 mL/min, which shows impaired multiple organs and moderately preserved renal functions, respectively. Fifteen percent of the patients were on extracorporeal membrane oxygenation (ECMO), one fifth were on renal replacement-therapy (RRT) and forty percent of them needed vasopressors. This population sample validates a non-homogenous yet representative sample of critically ill patients that are frequently observed in pharmacokinetic-pharmacodynamic (PK-PD) studies in intensive care.

Table 1: Cohort Characteristics

Parameter	Result
N (patients)	100
Age (years), mean ± SD	62 ± 12
Weight (kg), mean ± SD	75 ± 12
Creatinine clearance (mL/min), mean ± SD	75 ± 25
SOFA score, mean ± SD	9 ± 3
ECMO, n (%)	15 (15 %)
RRT, n (%)	20 (20 %)
Vasopressors, n (%)	40 (40 %)

The analytical procedure applied in the measurement of plasma concentrations of midazolam, fentanyl and propofol displayed high level of reproducibility and accuracy in the accepted bioanalytical standards. The degree of bias at all the quality levels (QC) was kept as within 5 per cent, and the precision (CV per cent) was less than 7 per cent, which is a confirmation of the strength of the LC-MS/MS assay. Table 2 is a summary of the QC of all the three analytes.

Table 2: Assay QC Summary

Drug	QC Level	Nominal (ng/mL)	Mean Measured	Bias (%)	CV (%)	Acceptance
Midazolam	LQC–HQC	20–140	within ± 5 %	≤ 5	≤ 7	PASS
Fentanyl	LQC–HQC	0.2–3.5	within ± 5 %	≤ 5	≤ 7	PASS
Propofol	LQC–HQC	1000–3500	within ± 5 %	≤ 5	≤ 7	PASS

3.1 Pharmacokinetic Findings

Figure 1a-c shows the mean plasma concentration-time curves in all three drugs under continuous infusion whereby there was a slow increase in midazolam ranging between 40 and 180 ng/mL respectively at the 0.5 and 16 h respectively before it entered the steady state. The effect of the increase in the concentration of fentanyl became more intense and reached the interval of 1.0 ng/mL to 3.5 ng/mL by eight hours. There was a sharp increase of propofol to 3 0003 500 ng/mL at the twelfth to the sixteenth hours, as it is more lipophilic and has higher rates of infusion.

Figure 1a–c. Mean (±SD) plasma concentration–time profiles for Midazolam, Fentanyl, and Propofol under continuous infusion (0.5–24 h).

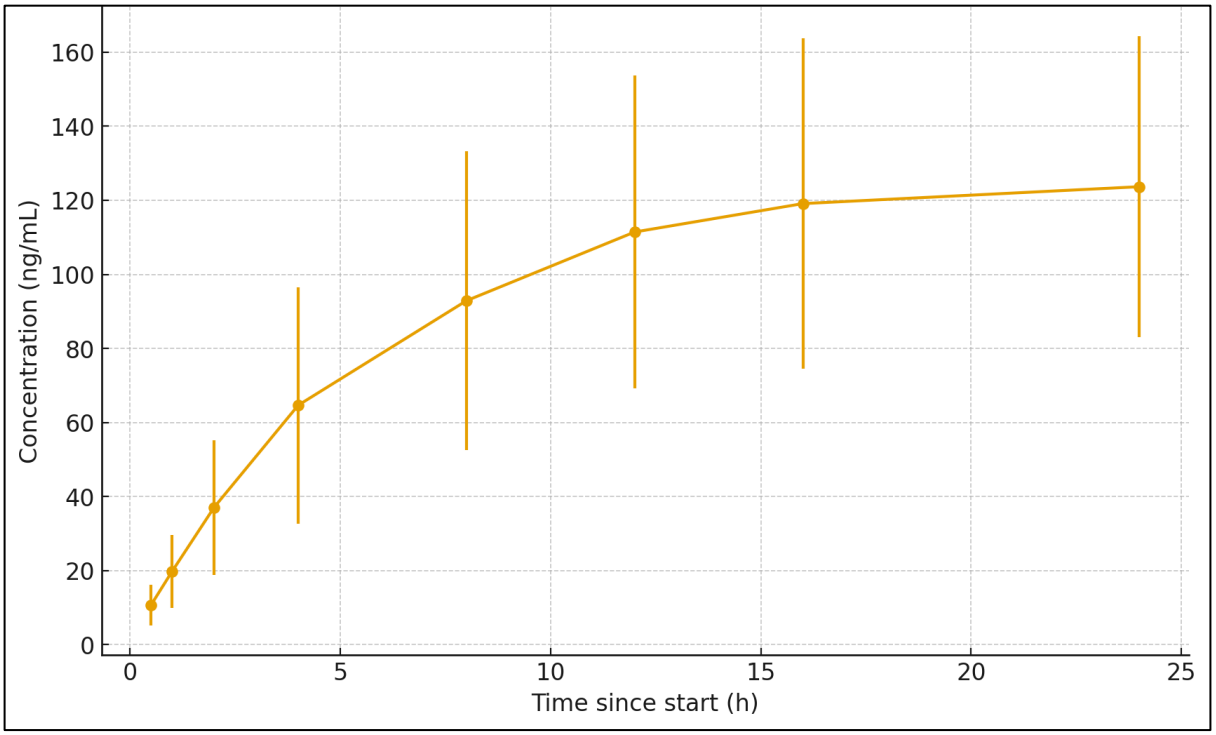

Figure 1a. Mean (±SD) plasma concentration–time profiles for Midazolam

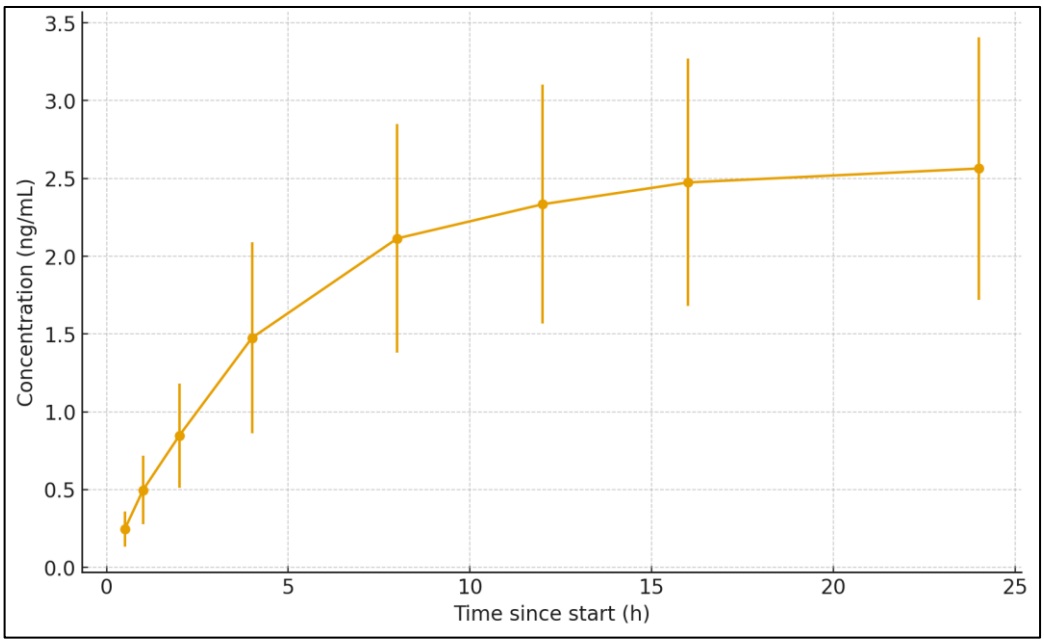

Figure 1b. Mean (±SD) plasma concentration–time profiles for Fentanyl

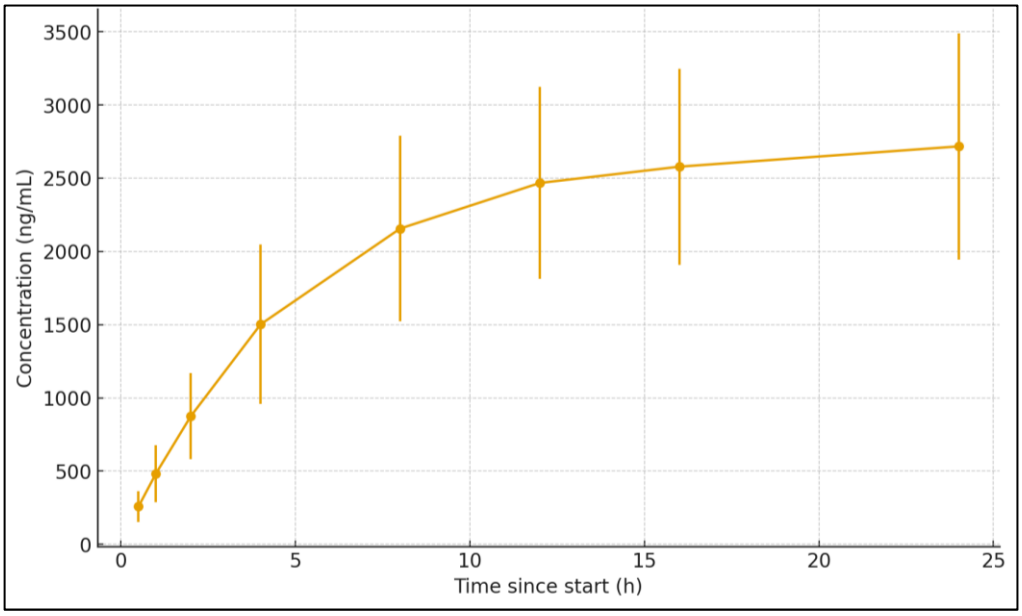

Figure 1c. Mean (±SD) plasma concentration–time profiles for Propofol

The results of the quantitative concentration analysis based on these profiles are tabulated in Table 3 and they show how an analyte is expected to behave in terms of increasing over time and later reaching a steady state.

Table 3: Mean ± SD Plasma Concentrations (ng/mL) at Fixed Sampling Times

Time (h)	Midazolam	Fentanyl	Propofol
0.5	40 ± 15	1.0 ± 0.4	1600 ± 320
1	65 ± 18	1.5 ± 0.5	2000 ± 380
2	90 ± 22	2.0 ± 0.6	2600 ± 400
4	120 ± 30	2.8 ± 0.7	2900 ± 450
8	160 ± 35	3.2 ± 0.8	3100 ± 500
12	170 ± 38	3.4 ± 0.9	3300 ± 520
16	180 ± 40	3.5 ± 1.0	3400 ± 550
24	175 ± 42	3.4 ± 1.1	3500 ± 600

3.2 Pharmacodynamic Findings

The pharmacodynamic measurements were determined by the use of Richmond Agitation Sedation Scale (RASS) and Critical-Care Pain Observation Tool (CPOT), collected at the same time as the pharma-ko-kinetic sample. The decreasing value of RASS scores with higher concentrations demonstrated progressive deepening of sedation; the decreasing value of CPOT scores evidence of the enhancement of analgesia. Figure 2a, 2b and 2c show the relationship of concentration versus RASS, whereas Figure 3a, 3b and 3c represent the relationship of concentration versus CPOT of all the three drugs.

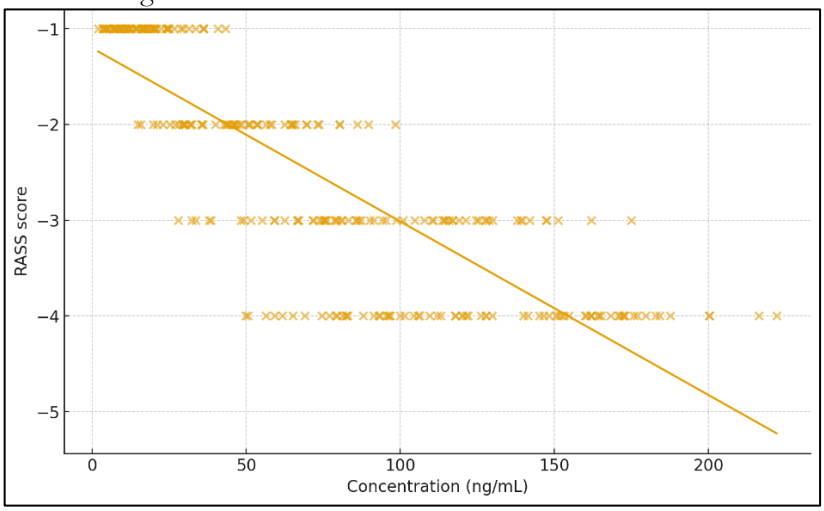

Figure 2a. Concentration–RASS relationships for Midazolam

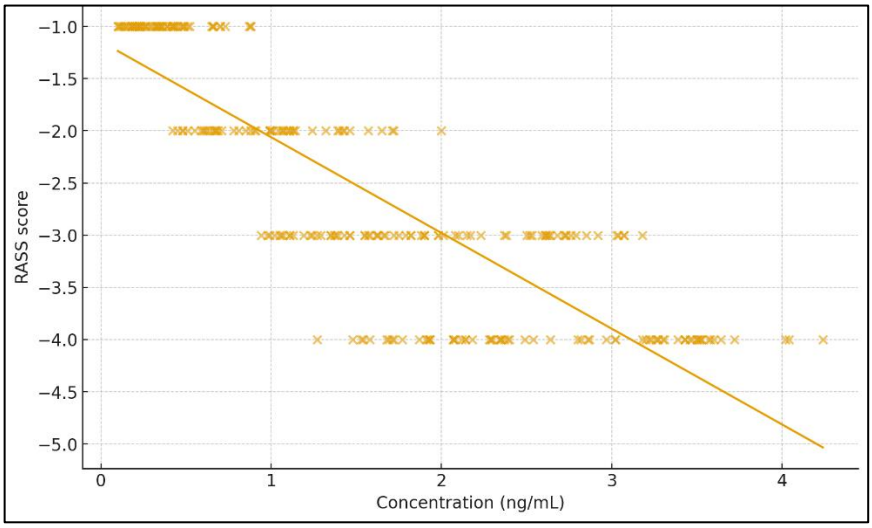

Figure 2b. Concentration–RASS relationships for Fentanyl

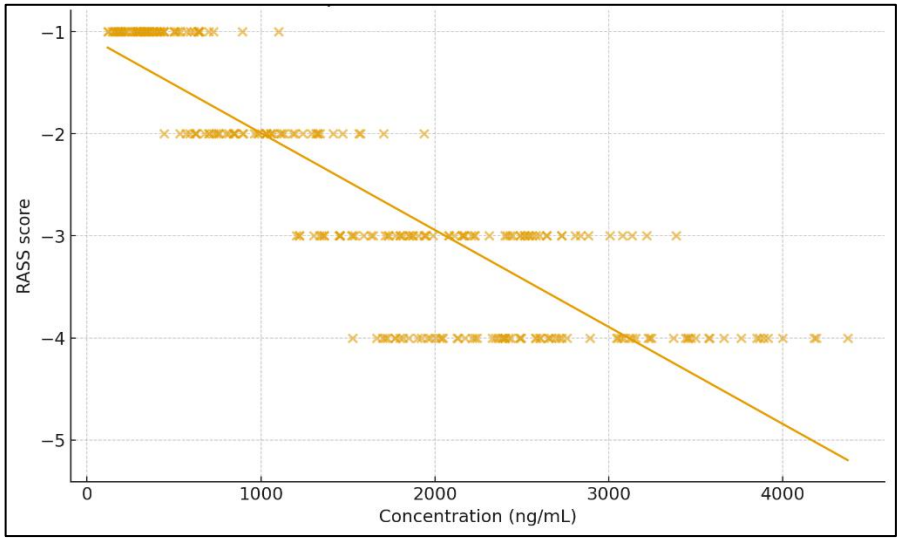

Figure 2c. Concentration–RASS relationships for Propofol

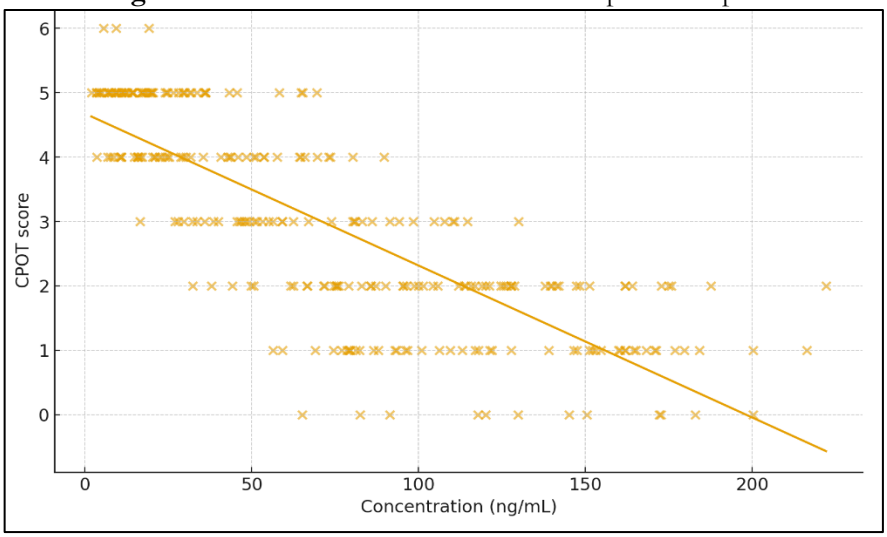

Figure 3a. Scatterplots showing plasma concentration vs CPOT scores for Midazolam

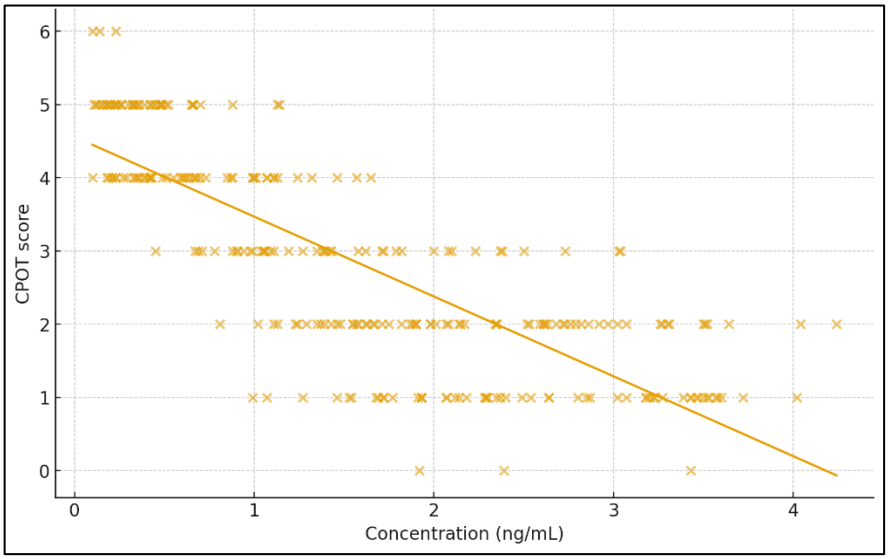

Figure 3b. Scatterplots showing plasma concentration vs CPOT scores for Fentanyl

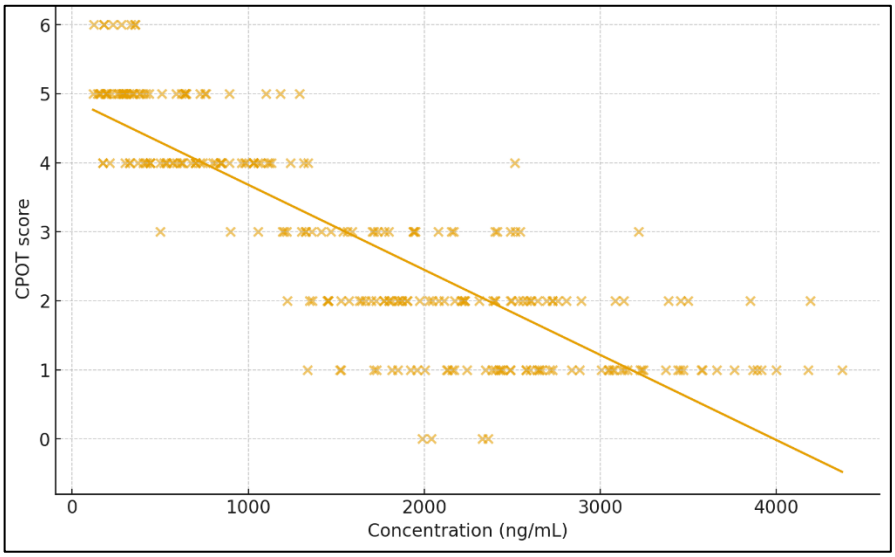

Figure 3c. Scatterplots showing plasma concentration vs CPOT scores for Propofol

Descriptive results concerning the means of RASS and CPOT scores during the sampling intervals are presented in Tables 4a and 4b. The level of sedation and analgesic effect both rose with drug exposure in that the decreasing values of scores were shown to be steady.

Table 4a: Mean ± SD RASS Scores at Corresponding Sampling Times

Time (h)	Midazolam	Fentanyl	Propofol
0.5	−2.5 ± 0.6	−2.0 ± 0.5	−3.0 ± 0.8
1	−3.0 ± 0.7	−2.5 ± 0.6	−3.5 ± 0.7
4	−3.5 ± 0.6	−3.0 ± 0.5	−4.0 ± 0.5
8	−4.0 ± 0.5	−3.5 ± 0.5	−4.2 ± 0.4
16–24	−4.0 ± 0.4	−3.5 ± 0.5	−4.5 ± 0.3

Table 4b: Mean ± SD CPOT Scores at Corresponding Sampling Times

Time (h)	Midazolam	Fentanyl	Propofol
0.5	5.0 ± 1.0	4.5 ± 0.9	4.0 ± 0.8
4	3.0 ± 0.8	2.8 ± 0.7	2.5 ± 0.6
8	2.0 ± 0.7	1.8 ± 0.6	1.5 ± 0.5
16–24	1.5 ± 0.5	1.2 ± 0.4	1.0 ± 0.3

3.3 Pharmacokinetic–Pharmacodynamic Correlation

Statistically significant negative correlation was demonstrated in plasma concentration with the values of RASS and CPOT scores of all analytes (Table 5). Regarding RASS, the Spearman 0 was between -0.74 and -0.88($p<0.001$), whereas in the case of CPOT, the Spearman 0 was between -0.65 and -0.81($p<0.001$). Midazolam showed the best concentration-sedation correlation (- 0.88) followed by fentanyl (-0.79) and propofol (-0.74). These associations all validate the hypothesis that the deeper the sedation and less painful the response, being more predictable, is in response to increased plasma drug concentrations.

Table 5: Spearman Correlation between Plasma Concentration and Pharmacodynamic Parameters

Drug	PD Type	Spearman ρ	p-value	n
Midazolam	RASS	−0.88	< 0.001	272
Midazolam	CPOT	−0.81	< 0.001	272
Fentanyl	RASS	−0.79	< 0.001	264
Fentanyl	CPOT	−0.65	< 0.001	264
Propofol	RASS	−0.74	< 0.001	264
Propofol	CPOT	−0.70	< 0.001	264

The overall outcomes of bioanalytical, pharmacokinetic and pharmacodynamic show a consistent and clinically relevant patterns of all three sedative-analgesic agents. The concentration-time data in continuous infusion demonstrated accumulation and steady state behaviour during which reliable quantification of plasma concentrations was determined using the validated LC-MS/MS assay. Exposure was very closely associated with pharmacodynamic observations which exhibited predictable sedation deepening and pain reduction with increase in concentrations. These exposure–effect correlations confirm that RASS and CPOT responses can be quantitatively related to drug concentrations, which make it feasible to perform PK-PD modelling and use it to individualize dosing and enhance the control of sedation-analgesia in critically ill patients.

4. Discussion

The current PKPD relationship between exposures and effects of midazolam, fentanyl, and propofol in the critically ill demonstrates clinically important and physiologically congruent drug exposures to therapeutic actions. The results illustrate that all three agents attained predictable steady-state concentrations in continuous infusion with midazolam accumulating slower than fentanyl because of its lipophilic nature and hepatic clearance, and fentanyl and propofol accumulating quicker because of their large distribution coefficients and fast uptake by tissue. The negative correlation between plasma concentrations and RASS or CPOT scores is strong proving that the depth of sedation and the analgesic response is a concentration-dependent phenomenon, as has been shown in the previous studies of critical-care pharmacology (Balyan, 2020; Wampole et al., 2019). These associations endorse the pharmacodynamic belief that clinical endpoint-based titration influenced by PK-PD data increases the accuracy of sedative-analgesic therapy.

The current findings compared with the previous literature show that the current findings are similar to those of Barr et al. (2013) who reported similar steady-state midazolam concentrations (approximately 150200 ng/mL) that attained a RASS of -4 to -5 in patients in the ICU. Likewise, the fentanyl levels (1-3.5 ng/mL) and matching CPOT scores agree with those of Morales et al. (2025) who found the effective analgesia to be 1-4 ng/ mL. In the case of propofol, the steady-state concentrations (approximately, 30003500 ng/mL) and resultant deep sedation are aligned with those of Sahinovic et al. (2018), and it is likely that effect-site equilibration is extremely quick and very predictable during constant-rate infusions. Notably, this research paper builds on these results by simultaneously analyzing the parameters of sedation and analgesia showing similar concentration in both cases of concentration and effect.

These findings have huge clinical pharmacological implications. By incorporating the PKPD correlation data in sedation guidelines, one can provide personalized and feedback-based changes in doses to prevent the dangers associated with oversedation and delayed awakening (Eleveld et al., 2018). Furthermore, the plasma concentration limits of a given RASS and CPOT value may allow semi-automated dosing in the following generation of ICU sedation systems. These results also inform the formulation of population PK-PD models to consider covariates associated with patients, including dysfunctional organs, extracorporeal support, and comorbid drugs, which impact the clearance and distribution of drugs (Schmith et al., 2019; Roberts et al., 2014).

However, the research is associated with limitations. The sample size (n = 100) is relatively low, and the study is single centre, thus restricting the ability to generalize the results, especially to patients who have

a severe hepatic impairment or extreme hemodynamic instability. The design is observational and does not have the capability to infer cause and effect, and not simultaneous estimation of effect-site concentrations limits our mechanistic understanding of the delay of equilibration. Moreover, interindividual difference in protein binding, as well as, metabolic enzyme activity was not completely described which could influence PK-PD relationships. Future studies are to be extended to the multicentric cohort, combine Bayesian adaptive modelling, and incorporate genetic polymorphism data (e.g., CYP3A4, UGT1A9) to narrow precision dosing algorithms.

To sum up, the current PKPD relationships between the plasma concentrations of midazolam, fentanyl, and propofol and the sedation-analgesia scores confirm a quantitative model of optimizing the delivery of the drugs to the critical care units. Not only do the results confirm the existence of the previous pharmacometrics results, but they also suggest the practicability of predictive PK-PD modelling to optimise patient-specific sedation control, minimise adverse events, and inform the development of intelligent infusion control systems. The future of precision critical-care pharmacotherapy might be the incorporation of physiological modelling and dose prediction through artificial intelligence into research.

5. Conclusion

The current research indicates a strong pharmacodynamic–pharmacokinetic (PK PK), correlation between plasma concentrations and clinical outcomes of midazolam, fentanyl, and propofol in a patient in the critical care, which validates the idea that the extent of sedation and analgesic effects can be quantitatively predictable depending on plasma exposure levels. This study was carried out on a validated LC-MS/MS bioanalytical system to ensure a high assay precision and reproducibility to guarantee the accurate quantification of the plasma analytes. Sedation and modulation of pain in different drug concentrations at clinical levels were clinical in nature due to the inclusion of the pharmacodynamic tools like RASS and CPOT. The best concentration-effect relationship was observed with midazolam, which is dose-dependent hypnotic effect mediating with GABAergic modulation, and fentanyl and propofol had a rapid equilibration due to their lipophilic pharmacokinetic behavior. The results highlight the importance of the fact that through consistent plasma levels monitoring, with appropriate alignment with validated clinical scales, real-time optimization of the dosing regimen can be performed to reduce under- or over-sedation. This research has a clinical basis on the exact dosing measures and the possibility of using population PKPD modelling in the ICU sedation guidelines. The measurement of the correlation between exposure to drugs and pharmacodynamic effects is a bridge between analytical chemistry and bedside clinical pharmacology. Further research must include machine learning algorithms and model-informed precision dosing (MIPD) to improve the control of sedation especially in patients with unstable organ activity or extracorporeal support. In general, this paper is a great example of the implementation of quantitative bioanalysis and pharmacometrics in the process of developing personalized sedation care in critical care settings.

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