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Suspected fentanyl–midazolam adverse drug reactions, mainly bradypnea and bradycardia, are associated with prolonged intensive care unit stay in mechanically ventilated patients

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ABSTRACT

Background: Fentanyl–midazolam remains a common analgosedation regimen for mechanically ventilated patients in many intensive care units (ICUs). Its adverse drug reactions (ADRs) may prolong ICU length of stay (LOS), but evidence is limited, particularly in Indonesia.

Objective: To describe suspected ADRs associated with fentanyl–midazolam and their association with ICU LOS in mechanically ventilated patients.

Methods: This retrospective cohort study reviewed records of adults receiving mechanical ventilation and continuous fentanyl–midazolam infusion in the ICU of an Indonesian academic hospital from January 2022 to April 2023. Of 460 patients screened, 80 were analyzed (40 with and 40 without suspected ADRs). Causality was assessed with the World Health Organization–Uppsala Monitoring Centre system and severity with the Hartwig scale. Prolonged LOS was defined as ≥3 days. Associations were tested with the chi-square test and expressed as risk ratios (RRs).

Results: Among the 40 patients with suspected ADRs, the most frequent reactions were bradypnea (17/40, 42.5%), bradycardia (14/40, 35.0%), and apnea (4/40, 10.0%). Causality was probable in 27 patients (67.5%) and possible in 13 (32.5%), and 36 reactions (90.0%) were Hartwig level 1. Prolonged LOS occurred in 32 of 40 patients (80.0%) with ADRs and 22 of 40 (55.0%) without ADRs (p = 0.017; RR 1.45; 95% CI 1.06–2.00).

Conclusion: Suspected fentanyl–midazolam ADRs, mostly mild respiratory depression and bradycardia, were associated with prolonged ICU stay. Close respiratory and hemodynamic monitoring and careful dose titration are warranted.

Keywords: adverse drug reaction, fentanyl, intensive care unit, length of stay, mechanical ventilation, midazolam

Introduction

An adverse drug reaction (ADR) is a noxious and unintended response to a medicine given at doses normally used in humans [1]. Critically ill patients are particularly vulnerable because they receive many drugs, have altered pharmacokinetics, and often cannot report symptoms. In one prospective ICU surveillance study, 28% of patients had an ADR, and invasive mechanical ventilation and polypharmacy were among the associated factors [2]. Mechanically ventilated patients need analgesia and sedation to remain comfortable and synchronous with the ventilator. The 2018 PADIS guideline recommends light sedation and favors propofol or dexmedetomidine over benzodiazepines [3].

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Even so, benzodiazepines remained the most common sedatives in Asia, Africa, and Latin America in a large international cohort [4]. Midazolam was also the most used sedative in South Korean ICUs [5]. The fentanyl–midazolam combination is therefore still widely used where non-benzodiazepine alternatives [6] are less accessible.

Opioids and benzodiazepines both depress ventilatory drive, and their combination raises the risk of respiratory and hemodynamic events. In a multinational prospective study, 46% of ward patients receiving parenteral opioids had at least one respiratory depression episode [7]. These patients stayed in hospital about 3 days longer. Concurrent opioid and benzodiazepine exposure in older trauma patients was associated with more unplanned intubations and longer hospital stay [8]. Among mechanically ventilated patients, benzodiazepine sedation has been linked to higher in-hospital mortality [9] and fewer delirium-free days after extubation [10]. In a Japanese ICU, adverse drug events were associated with longer ICU stay [11].

These studies examined sedative choice, sedation depth, or adverse events in general rather than the ADR profile of the fentanyl–midazolam combination. Indonesian evidence is also scarce. A study at the same hospital linked drug-related problems with LOS in patients with type 2 diabetes [12]. However, we found no Indonesian study that assessed ADRs from ICU analgosedation with a standardized causality tool. This study therefore aimed to describe suspected ADRs associated with fentanyl–midazolam in mechanically ventilated ICU patients and to evaluate their association with ICU LOS.

Methods

Study design and setting

This retrospective cohort study used electronic medical records from the ICU of the Academic Hospital of Universitas Gadjah Mada, Yogyakarta, Indonesia. Records from January 2022 to April 2023 were reviewed. The unit of analysis was the patient, and each patient contributed one ICU admission. The study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada (approval number KE/FK/0296/EC/2023). Although the initial ethical approval included informed consent protocols, the study was ultimately conducted purely as a retrospective analysis using existing electronic records without direct patient contact. All data were fully anonymized prior to analysis.

Patients and sample

Eligible patients were adults (⩾18 years) who received invasive mechanical ventilation and a continuous fentanyl–midazolam infusion during ICU admission. Patients were excluded if they were pregnant, received neuromuscular blocking agents, had a baseline systolic blood pressure <80 mmHg or heart rate <40 beats/min before therapy, or died prior to therapy initiation. These criteria ensured that observed respiratory or hemodynamic events could reasonably be attributed to the study drugs. Of the 460 patients screened, 398 met the inclusion criteria. Based on Lemeshow's formula for two independent proportions, the required minimum sample size was 40 patients per group. Consecutively, 40 patients with suspected ADRs and 40 patients without suspected ADRs were selected, resulting in a final sample of 80 patients for analysis

Exposure, causality, and severity assessment

The exposure was a suspected ADR during fentanyl–midazolam infusion. Only events occurring after infusion initiation or following a dose increase were considered. Operational thresholds for suspected ADRs were defined as follows: **hypotension** as a >25% reduction in mean arterial pressure (MAP) from baseline or a systolic blood pressure <80 mmHg; **bradycardia** as a >20 beats/min drop in heart rate from baseline or a heart rate <60 beats/min; **bradypnea** as a respiratory rate <12 breaths/min; and **apnea** as clinician documented cessation of breathing. Other reported events, including **agitation** and **dry mouth**, were identified based on explicit clinical documentation in medical or nursing notes.

Causality was assessed with the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) system [1] and and was subsequently validated independently by a clinical pharmacist specialist. Any discrepancies in causality classification were resolved through discussion and consensus. Patients with causality categories of certain, probable, or possible were assigned to the ADR group, whereas patients with no suspected adverse events or events classified as unlikely were assigned to the non-ADR group

Fentanyl and midazolam were co-infused as one analgosedation regimen and have overlapping

Table 1. Baseline characteristics of mechanically ventilated patients by suspected ADR status

Characteristic	Group		p value
	ADR (n = 40)	Non-ADR (n = 40)	
Sex, n (%)			
Male	27 (67.5)	14 (35.0)	0.004[a]
Female	13 (32.5)	26 (65.0)	
Age (years)			
Mean ± SD	51.20 ± 14.54	56.38 ± 13.32	0.07[b]
BMI (kg/m²)			
Mean ± SD	23.10 ± 5.04	23.30 ± 3.61	0.33[b]
APACHE II score			
Mean ± SD	11.85 ± 2.97	12.60 ± 2.69	0.23[b]
CCI score			
Mean ± SD	0.43 ± 0.81	0.40 ± 0.77	0.93[b]

Data are per patient (n = 80). Values are n (%) or mean ± SD; percentages use the group total (n = 40) as the denominator. [a]Pearson chi-square test. [b]Mann–Whitney U test. ADR, adverse drug reaction; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCI, Charlson Comorbidity Index; SD, standard deviation.

depressant effects on the central nervous and respiratory systems. Causality was therefore attributed to the combination rather than to either drug alone. All concomitant drugs were reviewed to exclude alternative causes, such as other sedatives, neuromuscular blockers, and antihypertensives. The pharmacodynamic interaction between fentanyl and midazolam was considered under the WHO-UMC plausibility criterion.

ADR severity was graded with the Hartwig scale [13], whose Indonesian version has been validated [14]. Baseline disease severity was measured with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [15]. Comorbidity burden was measured with the Charlson Comorbidity Index (CCI) [16].

Outcome and statistical analysis

The primary outcome was ICU LOS in days. LOS was dichotomized into short (<3 days) and prolonged (⩾3 days) stays at the cohort mean of 3.0 days. This short cut-off reflects the case mix, which consisted mainly of elective post-surgical patients requiring short-term ventilation.

Data were analyzed with using IBM SPSS Statistics, version 27.0.

Categorical variables are presented as n (%), with the number of patients in each group (n = 40) as the denominator. Continuous variables are presented as mean ± standard deviation (SD). Sex was compared with the chi-square test. Age, body mass index (BMI), APACHE II, and CCI were compared with the Mann–Whitney U test because they were not normally distributed. The association between ADR status and prolonged LOS was tested with Pearson's chi-square test without continuity correction, because all expected cell counts exceeded 5. The association was expressed as a risk ratio (RR) with 95% confidence interval (CI). Simple binary logistic regression estimated odds ratios (ORs) for prolonged LOS. Age, APACHE II, and CCI were analyzed in all patients (n = 80). Hartwig severity level and number of ADRs per patient were analyzed within the ADR group (n = 40). Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Of the 80 patients analyzed, 40 had suspected ADRs and 40 did not. Men made up a larger proportion of the ADR group than of the non-ADR group (27/40, 67.5% vs 14/40, 35.0%; p = 0.004). The groups did not differ in age (51.20 ± 14.54 vs 56.38 ± 13.32 years; p = 0.07) or BMI (23.10 ± 5.04 vs 23.30 ± 3.61 kg/m²; p = 0.33). APACHE II score (11.85 ± 2.97 vs 12.60 ± 2.69; p = 0.23) and CCI score (0.43 ± 0.81 vs 0.40 ± 0.77; p = 0.93) were also similar (Table 1).

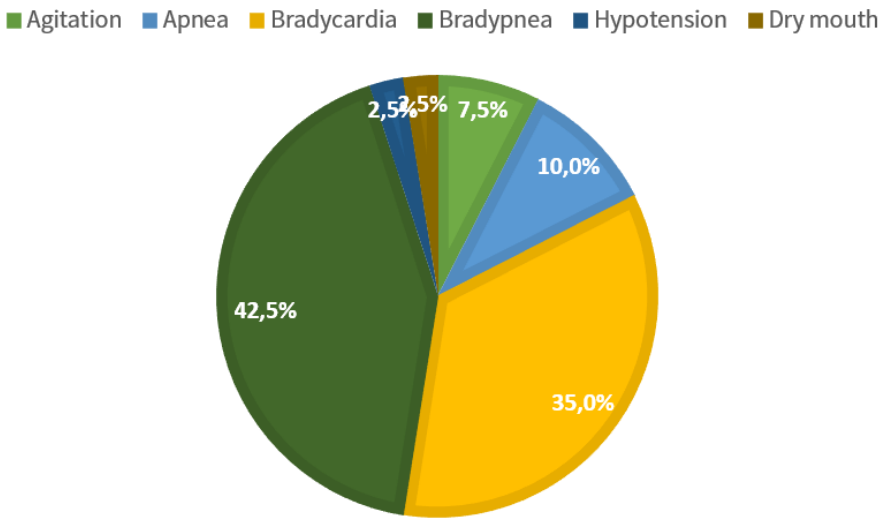


Figure 1. Distribution of suspected ADRs among patients receiving fentanyl–midazolam (n = 40). Percentages use the 40 patients with suspected ADRs as the denominator

Table 2. ICU length of stay by suspected ADR status

Group	ICU length of stay, n (%)		p value
	≥3 days	<3 days	
With ADR (n = 40)	32 (80.0)	8 (20.0)	0.017[a]
Without ADR (n = 40)	22 (55.0)	18 (45.0)	

Data are per patient (n = 80). Values are n (%), with the group total (n = 40) as the denominator. [a]Pearson chi-square test without continuity correction; RR 1.45 (95% CI 1.06–2.00). ADR, adverse drug reaction; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; RR, risk ratio.

Fentanyl–midazolam administration

Both groups received fentanyl at 2–24 µg/h and midazolam at 0.1–1 mg/h, titrated individually to clinical response. Dose titration produced greater variability in the ADR group. In 14 of the 40 patients with ADRs (35.0%), the suspected ADR followed a dose increase.

Suspected adverse drug reactions

Among the 40 patients with suspected ADRs, the most frequent reactions were bradypnea (17/40, 42.5%) and bradycardia (14/40, 35.0%). These were followed by apnea (4/40, 10.0%), agitation (3/40, 7.5%), hypotension (1/40, 2.5%), and dry mouth (1/40, 2.5%) (Figure 1). Causality was probable in 27 patients (67.5%) and possible in 13 (32.5%), and no case was classified as certain.

Most reactions (36/40, 90.0%) were Hartwig level 1 and required no change in the regimen. The other four (10.0%) were level 2 and required dose interruption, temporary discontinuation, or substitution, without an antidote or other additional treatment.

Adverse drug reactions and ICU length of stay

The mean ICU LOS in the whole cohort was 3.0 days, and most patients stayed 2–3 days. Prolonged LOS (≥3 days) occurred in 32 of 40 patients with ADRs (80.0%) and in 22 of 40 patients without ADRs (55.0%) (Table 2). The difference was significant (χ^2 = 5.70; p = 0.017). Patients with suspected ADRs had a 1.45-fold higher risk of prolonged LOS (RR 1.45; 95% CI 1.06–2.00).

Other clinical factors and ICU length of stay

None of the clinical factors examined was associated with prolonged LOS (Table 3). Age (OR 1.00; 95% CI 0.97–1.03; p = 0.78) and APACHE II score (OR 0.93; 95% CI 0.78–1.10; p = 0.40) showed no association. Neither did CCI score (OR 1.22; 95% CI 0.68–2.17; p = 0.49). Within the ADR group, Hartwig severity level

Table 3. Univariable association of clinical factors with prolonged ICU length of stay (≥3 days)

Variable	p value	OR (95% CI)
Age (per year)	0.78	1.00 (0.97–1.03)
APACHE II score (per point)	0.40	0.93 (0.78–1.10)
CCI score (per point)	0.49	1.22 (0.68–2.17)
Hartwig severity level[a]	0.050	0.42 (0.18–1.02)
Number of ADRs per patient[a]	0.19	0.62 (0.30–1.26)

Simple binary logistic regression. Age, APACHE II, and CCI were analyzed in all patients (n = 80). [a]Analyzed within the ADR group (n = 40). ADR, adverse drug reaction; APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

was not significantly associated with prolonged LOS (OR 0.42; 95% CI 0.18–1.02; p = 0.050). These analyses were unadjusted, so they do not show whether the ADR–LOS association is independent of other factors.

Discussion

Three main findings emerged from this cohort. Suspected ADRs during fentanyl–midazolam infusion were dominated by bradypnea and bradycardia. Most reactions were mild and had probable causality. Patients with these reactions were 1.45 times more likely than those without to stay in the ICU for 3 days or longer.

Respiratory and cardiovascular events accounted for 36 of the 40 reactions (90.0%). This pattern fits the pharmacology of the combination. Midazolam enhances GABA-mediated inhibition, whereas fentanyl acts on μ-opioid receptors in the brainstem respiratory centers. Together they reduce respiratory rate and tidal volume and may cause apnea [3,7]. Fentanyl-induced vagal stimulation and midazolam-related loss of sympathetic tone can also produce bradycardia and hypotension. Bradyarrhythmias were likewise among the most frequent ADRs leading to ICU admission in a Colombian university hospital [17]. In an Indian medical ICU, most ADRs were electrolyte disturbances and were mainly moderate on the Hartwig scale [18]. The milder profile in our cohort probably reflects a single drug combination and early detection under continuous ICU monitoring. Agitation may represent a paradoxical reaction to midazolam, and dry mouth is a recognized effect of xerogenic medications [19].

These reactions should not be regarded as an unavoidable cost of sedation. The PADIS guideline discourages benzodiazepine-based sedation in mechanically ventilated adults [3], and benzodiazepine sedation has been associated with higher mortality [9] and delirium [10]. The ADRs observed here are, in part, predictable consequences of a regimen that current guidelines do not favor. Where dexmedetomidine or propofol is available [6], it should be considered, particularly for patients at high risk of respiratory depression.

The association between ADRs and prolonged ICU stay agrees with earlier studies. Adverse drug events were associated with longer ICU stay in a Japanese ICU [11], and ICU patients with ADRs in India stayed substantially longer [18]. Opioid-related respiratory depression and combined opioid–benzodiazepine exposure have also been linked to longer hospitalization [7,8]. Even mild bradypnea or apnea may delay weaning and extubation, and bradycardia requires observation before transfer. Reverse causation is an alternative explanation. Patients who stay longer receive the infusion for longer and have more opportunity to develop an ADR. Hartwig severity was not associated with prolonged LOS, and its OR was below 1. With only four level 2 reactions, this estimate is imprecise and should not be interpreted as a protective effect.

Men were overrepresented in the ADR group. A higher ADR incidence in men was also reported in an Indian ICU [18]. In contrast, pharmacovigilance data and an Indonesian geriatric cohort found more ADRs in women [20,21]. The sex effect therefore appears to depend on setting and drug, and in our cohort it may reflect case mix rather than susceptibility. Age did not differ between groups, and the ADR group was slightly younger, unlike studies of older inpatients in which ADRs were common [22]. APACHE II and CCI were also similar. In a Brazilian geriatric ICU, severity scores likewise did not predict ADRs [23]. Drug exposure and monitoring intensity may matter more than baseline severity. Polypharmacy and drug–drug interactions are

known contributors to ADRs [21,24], but concomitant medications were not quantified here.

This study has limitations that affect interpretation of the main finding. ADR status was treated as fixed, although ADRs occurred during the ICU stay. The association with LOS may therefore partly reflect longer exposure rather than an effect of the ADR. The associations were also unadjusted, and sex, type of surgery, primary diagnosis, infusion duration, and dose may confound them. Retrospective records may have missed mild events, and sedation depth scores were not analyzed. The 3-day cut-off reflects this predominantly post-surgical cohort and may not apply to medical ICUs. The single-center design, small sample, and fixed group sizes limit generalizability, and the proportions reported describe this sample rather than incidence. Future prospective multicenter studies should record sedation scores and infusion doses daily and model ADRs as time-dependent exposures. They should also adjust for case mix and compare fentanyl–midazolam with dexmedetomidine- or propofol-based regimens.

Conclusion

In mechanically ventilated ICU patients receiving fentanyl–midazolam, suspected ADRs were mainly bradypnea (42.5%) and bradycardia (35.0%), and most were mild with probable causality. Patients with these reactions were more likely to stay in the ICU for 3 days or longer (80.0% vs 55.0%; RR 1.45; 95% CI 1.06–2.00). Close respiratory and hemodynamic monitoring, cautious dose titration, and consideration of non-benzodiazepine sedation may reduce these reactions and their effect on ICU stay.

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The authors have no acknowledgements to declare.

Conflict of Interest

The authors declare no conflict of interest.

Author contributions

WS: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. IPS: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. TMA: Conceptualization, Methodology, Supervision, Writing – review & editing. All authors approved the final manuscript.

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Declaration of generative AI use

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