

## Safety profile of remifentanil: A post-marketing study in Indonesia

Jarir At Thobari<sup>1,2\*</sup> , Jonathan Hasian Haposan<sup>2</sup> , Lukman Ade Chandra<sup>1,2</sup>, Nastia Hidayati<sup>3</sup> , Rianiasa Karunia Dewi<sup>3</sup>, Rita Wahyu Purnamasari<sup>3</sup>, Dyah Juliana Pudjiati<sup>3</sup>

<sup>1</sup>Department of Pharmacology & Therapy, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

<sup>2</sup>Clinical Epidemiology & Biostatistics Unit, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

<sup>3</sup>PT Kimia Farma, Jakarta, Indonesia.

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### ABSTRACT

Remifentanil is a novel short-acting  $\mu$ -opioid receptor agonist. Hence, it can be used as an alternative to fentanyl with additional short-acting potential. However, the safety profile of remifentanil in the Indonesian population through post-marketing surveillance has not been evaluated yet. Therefore, this study aims to evaluate the safety profiles of remifentanil in a multicenter pharmacovigilance study in Indonesia. There were 42 patients who used remifentanil during the 3 months of observation in six referral hospitals in Indonesia. It was found that 35 patients (83%) experienced at least one adverse event. There were 54 adverse events recorded during the observations, with hypotension and bradycardia being the most common adverse events, followed by nausea, respiratory depression, dizziness, shivering, warm sensation, and muscle rigidity. Based on the previous safety data, most of these adverse events were recognized as common adverse drug reactions of remifentanil. The expert panel meeting concluded that, from those adverse events, 98% were possibly related to remifentanil and only one adverse event was unlikely related. Based on this pharmacovigilance study, there are no additional safety concerns related to remifentanil as an analgesic and sedative drug indicated for patients on intubation, invasive mechanical ventilation, and noninvasive ventilation.

### INTRODUCTION

Remifentanil is a novel short-acting  $\mu$ -opioid receptor agonist with a similar analgesic and sedative potency as fentanyl (Burkle *et al.*, 1996). However, remifentanil is rapidly metabolized and has a very short duration of action (Egan *et al.*, 1993; Joshi *et al.*, 2002). Remifentanil has a rapid onset of action (about 1 minute) and a rapid offset of action following discontinuation (about 3–10 minutes) (Battershill and Keating, 2006). Remifentanil is approximately 70% bound to plasma proteins, and its average clearance of remifentanil is about 40 ml/minute/kg (Kimia Farma, 2019). Around the world, remifentanil is mainly used for

induction and maintenance in general anesthesia (Scott and Perry, 2005) and as an analgesic and sedative in the intensive care unit setting (Battershill and Keating, 2006). Remifentanil's rapid peak impact in the operating room makes it easier for users to perceive the anesthetic effect's dose-effect relationship. The quick onset of remifentanil also aids in detecting the presence of an excessive dose, which manifests as hypotension, hypoventilation, and bradycardia shortly after administration (Scott and Perry, 2005).

Based on a large post-marketing phase IV study in the US, adverse events following the administration of remifentanil are similar to those after fentanyl (Joshi *et al.*, 2002). Compared to fentanyl, remifentanil has organ independent mode of metabolism, which makes a good choice of opioid for use in renal-impaired patients (Muellejans *et al.*, 2004). Furthermore, a meta-analysis of the randomized controlled trial (RCT) suggested that remifentanil can benefit cardiac surgery with a decreased mechanical ventilation duration, cardiac biomarker release, and hospitalization duration. Hence, remifentanil can be used as an alternative to fentanyl with the additional advantages of short-acting potency and organ independent mode of metabolism (Greco *et al.*, 2012). However,

#### \*Corresponding Author

Jarir At Thobari, Department of Pharmacology & Therapy, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Clinical Epidemiology & Biostatistics Unit, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

E-mail: [j.atthobari@ugm.ac.id](mailto:j.atthobari@ugm.ac.id)

it was suggested that remifentanyl has a higher risk of hypotension compared to fentanyl (Joshi *et al.*, 2002), and the safety profile of remifentanyl in the Indonesian population through a post-marketing study has not been evaluated yet. Therefore, this study aims to evaluate the safety profiles of remifentanyl in a multicenter pharmacovigilance study in Indonesia.

## MATERIALS AND METHODS

A post-marketing study of remifentanyl was conducted in six referral hospitals in Indonesia (three hospitals in Jakarta, two in Surabaya, and one in Banjarmasin) during the period of June–September 2019. The use of remifentanyl and its adverse events were observed until discharge. The remifentanyl used in this study was in a concentrate powder for a solution with vial packages of 1, 2, and 5 mg of remifentanyl hydrochloride. Remifentanyl must be further diluted after reconstitution. The administration route was via a continuous infusion recommended with an infusion device (Kimia Farma, 2019).

The design of this study is a single-arm cohort study that targeted two types of hospitalized patients for whom remifentanyl was indicated, which include patients on intubation or invasive mechanical ventilation and patients on noninvasive ventilation (NIV). For patients who are intubated or on invasive mechanical ventilation, remifentanyl is used for its sedative and analgesic properties and as an alternative to fentanyl. The dose used for this type of indication is 0.05–0.5 mg/kg/minute with a 100 mg/ml concentration solution and close monitoring due to potential reduced respiratory drive. Patients on NIV and patients with Richmond Agitation-Sedation Scale (RASS) >0 and who are non-compliant with NIV can have remifentanyl. This may help with compliance with therapy and prevent the need for intubation. The dose used for this indication is 0.01–0.15 mg/kg/minute with a 50 mg/ml concentration. The absolute contraindication of the use of remifentanyl includes previous anaphylaxis/allergy to remifentanyl or fentanyl analogs. The relative contraindications among patients on intubation or invasive mechanical ventilation include hypotension and bradycardia (pulse rate < 50 bpm), while the relative contraindications among patients on NIV include RASS <0, reduced respiratory rate (RR < 10 times/minute), hypotension, and bradycardia. Investigators observed any adverse event that occurred within five consecutive days. Study nurses monitored the vital signs closely while patients were asked to report any symptoms. Provided with the details of health records and concomitant medications, the expert panel team assessed the causality of adverse events using the modified World Health Organization-Uppsala Monitoring Center system that consists of six categories: certain, probable, possible, unlikely, unclassified, and unassessable.

Using a Poisson distribution, power of 80%, and assumed risk ratio of occurring adverse events of 1.5, we calculated the sample size of a minimum of 36 patients. The baseline characteristics, including comorbidity events, were collected, and then the drug administration details (dose, route of administration, and device use) were collected during follow-up. Finally, all adverse events and management from health records and patient reports were recorded as the endpoints. We also collected concomitant medications during the follow-up to address potential sources of bias or confounding factors. All missing data were recorded and reported as missing and were not included in

the analysis. At the same time, all lost-to-follow-up patients were still analyzed and reported for any available data. No sensitivity and subgroup analyses were conducted in this study.

## RESULTS

### Baseline characteristics

There were 42 patients between June and September 2019 included in this Post Marketing Surveillance (PMS) of remifentanyl. The patients were mostly adult, with mean age 43.9 years, at a balance between male and female, mostly recorded from Pusat Otak Nasional (PON) Hospital (41%), with mostly neurological and malignancy main diagnosis (57%). No lost-to-follow-up patients were reported. Comorbidities were present in up to one-third of all participants, with the highest proportion being those with diabetes and cardiovascular diseases such as hypertension, heart disease, and arterial diseases (55%). The characteristics of patients who used remifentanyl in this post-marketing study can be seen in Table 1.

### Drug administration

The characteristics of remifentanyl used during this post-marketing study were mostly with dosage 2 mg (64.3%), using it with a device (90.5%), and administering it through injection or infusion. The dose package used by the hospitals was mostly one dose (66.7%). The characteristic use of remifentanyl can be seen in Table 2.

### Concomitant medications

There were 11 types of anesthetic agents concomitantly used with remifentanyl during the PMS, which are included into five subclasses of agents. A total of 114 drugs have been administered. There were 71 (62.3%) of these drugs used with a device and 43 (37.7%) without, with 107 drugs (94%) administered parenterally and seven drugs (6%) given by inhalation. Duration of use (in minutes) of these anesthetic drugs was 1 minute (minimum-maximum: 1–335 minutes). The type of the anesthetic drugs used during surgery can be seen in Table 3.

There were 24 types of concomitant medications used during the PMS, which are included in nine classes of agents. A total of 84 drugs have been administered and were mostly administered parenterally (94%), and only five drugs (6%) were given orally. The duration of use of these comedications was 1 day (minimum-maximum: 1–2 days). The type of other concomitant medications used during surgery can be seen in Table 4.

### Safety profile

There were 54 adverse events recorded in 35 out of 42 patients (83%) during the observation period, or 1.3 adverse events per observed patient. There were a total of 13 types of adverse events. In this study, the severity of the adverse events was not recorded. The types of adverse events during the use of remifentanyl can be seen in Table 5.

Table 6 explains how the anesthetist/physician managed the adverse events that occurred during the use of remifentanyl. Most patients with adverse events were not receiving additional treatment and others were receiving additional treatment or prolonged hospitalization. Most of the physicians reduced the dose during surgery, and one out of five patients stopped using

**Table 1.** Baseline characteristics of patients.

No	Characteristics	Results
1	Age (years), mean $\pm$ SD	43.9 $\pm$ 17.4
2	Sex, <i>n</i> (%)	
	Male	20 (47.6)
	Female	22 (52.4)
3	Main diagnosis, <i>n</i> (%)	
	Neurological	23 (54.8)
	Musculoskeletal	6 (14.3)
	Gastrointestinal	4 (9.5)
	Cardiovascular	3 (7.1)
	Endocrine	2 (4.8)
	Ear, nose, and throat	2 (4.8)
	Respiratory	1 (2.4)
	Dental	1 (2.4)
4	Comorbidity events, <i>n</i> (%)	22
	Number of patients	13
	One comorbidity	7 (53.8)
	More than two comorbidities	6 (41.2)
	Type of comorbidity	
	Hypertension	6 (27.2)
	Heart disease	4 (18.2)
	Chronic arterial disease	3 (13.6)
	Neurological disorder	2 (9.1)
	Diabetes Mellitus (DM)	2 (9.1)
	Pneumonia	2 (9.1)
	Cancer	1 (4.5)
	Cirrhosis	1 (4.5)
	Kidney failure	1 (4.5)

remifentanyl. There is no information on how much the dosages have been reduced for each patient with this adverse event (AE). Almost all patients were cured of these adverse events without any sequelae, and 67% of patients were discharged from the hospital.

## DISCUSSION

Among 42 patients who used remifentanyl within the 3 months in 6 hospitals, we found 35 patients (83%) have experienced at least one adverse event. This proportion was higher than the one was found in another phase IV study by *Joshi et al.* (2002), where about 52% of the inpatients using remifentanyl had at least one adverse event (*Joshi et al.*, 2002). There were 54 adverse events recorded during the observations, with hypotension and bradycardia being the most common adverse events, followed by nausea, respiratory depression, dizziness, shivering, warm sensation, and muscle rigidity. Despite a long list of adverse events, the risk of serious adverse events which need further management appears to be low in this study, with less than 5% of the total incidence. Most of the adverse events (59.5% of patients)

**Table 2.** Drug administration characteristics.

No	Drug administration characteristics	Results
1	Dose, <i>n</i> (%)	
	1 mg	15 (35.7)
	2 mg	27 (64.3)
2	Infusion device use, <i>n</i> (%)	
	With infusion device	38 (90.5)
	Without infusion device	4 (9.5)
3	Route of administration, <i>n</i> (%)	
	Injection	27 (64.3)
	Infusion	15 (35.7)
4	Dose package, <i>n</i> (%)	
	1 dose	28 (66.7)
	2 doses	14 (33.3)
5	Duration of administration, median (minutes–maximum)	201.0 (9–610)

**Table 3.** Concurrent anesthetic drugs.

No	Anesthetic drugs	<i>N</i> (%)
1	General anesthetics: halogenated hydrocarbons	
	1a. Sevoflurane	6 (5.3)
	1b. Desflurane	1 (0.9)
	1c. Isoflurane	1 (0.9)
2	General anesthetics: opioid anesthetics	
	2a. Fentanyl	13 (11.4)
	2b. Oxycodone	1 (0.9)
3	Muscle relaxant	
	3a. Rocuronium	32 (28.1)
	3b. Vecuronium	5 (4.4)
	3c. Atracurium	1 (0.9)
4	Hypnotic sedative	
	4a. Midazolam	16 (14.0)
	4b. Dexmedetomidine	3 (2.6)
5	Other general anesthetics	
	5a. Propofol	35 (30.7)

that occurred did not need further treatment/management in this study. However, there were eight (19%) patients who needed to stop remifentanyl. The expert panel meeting concluded that, from those adverse events, 98% were possibly related to remifentanyl and only one adverse event was unlikely related.

Among these adverse events, hypotension and bradycardia have the commonest occurrence in this study, contributing 37.0% and 27.8%, respectively. These proportions are higher than what *Joshi et al.* (2002) found, where hypotension and bradycardia occurred among 477 inpatient surgeries using remifentanyl at percentages of only 18% and 3%, respectively (*Joshi et al.*, 2002). However, a study by *Myles et al.* (2002) with

**Table 4.** Concomitant medications recorded during observation.

No	Concomitant medications	N (%)
1	Opioid analgesic	
	1a. Oxycodone	4 (4.8)
	1b. Tramadol	3 (3.6)
	1d. Morphine	2 (2.4)
	1e. Pethidine	1 (1.2)
2	Nonopioid analgesic	
	2a. Paracetamol	9 (10.7)
	2b. Ketorolac	6 (7.1)
	2c. Tranexamic acid	3 (3.6)
	2d. Ketoprofen	2 (2.4)
3	Antibiotics	
	3a. Cefazolin	15 (17.9)
	3b. Fosfomycin	1 (1.2)
	3c. Metronidazole	1 (1.2)
	3d. Gentamycin	1 (1.2)
	3e. Ceftriaxone	1 (1.2)
4	Antiemetic and antiulcer	
	4a. Ondansetron	11 (13.1)
	4b. Metoclopramide	4 (4.8)
	4c. Ranitidine	4 (4.8)
5	Antihypertensive	
	5a. Amlodipine	2 (2.4)
	5b. Bisoprolol	1 (1.2)
	5c. Captopril	1 (1.2)
6	Corticosteroid	
	6a. Dexamethasone	6 (7.1)
7	Blood substitutions	
	7a. Mannitol	5 (6.0)
8	Vasoconstrictions	
	8a. Ephedrine	1 (1.2)
9	Anticonvulsant	
	9a. Valproic acid	1 (1.2)

a small number of patients also found higher proportions, where 17% of patients had bradycardia and 66% patients had hypotension following remifentanyl administration intraoperatively (Myles *et al.*, 2002). Hypotension and bradycardia are actually more common in remifentanyl than in other kinds of anesthesia. Komatsu *et al.* (2007) found that when remifentanyl is used as a general anesthetic, the risk of bradycardia and hypotension is doubled, compared to other short-acting opioids such as fentanyl, alfentanil, or sufentanil (Komatsu *et al.*, 2007). However, these hemodynamic events seem to be dose-dependent (Joshi *et al.*, 2002). Therefore, close monitoring with the higher and lower doses is recommended during the administration of remifentanyl. There is no difference in the occurrence of mild adverse events

**Table 5.** The adverse events reported.

No	Type of events	N (%)	Duration in minutes median (minutes–maximum)
1	Respiratory		
	Respiratory depression	2 (3.7)	109.5 (1–218)
	Thorax rigidity	1 (1.9)	1
2	Cardiovascular		
	Hypotension	20 (37.0)	19.0 (1–278)
	Bradycardia	16 (27.8)	28.5 (1–310)
3	Genitourinary		
	Polyuria	3 (5.6)	167.0 (30–540)
4	Gastrohepatic		
	Abdominal discomfort	1 (1.9)	50
	Nausea	5 (9.3)	5.0 (5–70)
5	Musculoskeletal		
	Muscle stiffness	1 (1.9)	2
6	Nervous system		
	Dizziness	1 (1.9)	20
	Headache	1 (1.9)	5
7	Hematologic events		
	Leukocytosis	1 (1.9)	27
8	Others		
	Shivering	2 (3.7)	25.0 (15–35)
	Sensation of warm	1 (1.9)	120

such as nausea and vomiting between remifentanyl and other agents (Komatsu *et al.*, 2007).

In this study, thorax and muscle rigidity occurred in two (3.8%) remifentanyl-treated patients. The concern of thorax and muscle rigidity is lower based on another large multicenter phase IV study where four (0.3%) remifentanyl-treated patients experienced thorax and muscle rigidity compared to none among patients treated with fentanyl (Joshi *et al.*, 2002). Post-marketing surveillance is important because of the range of observed patients and the capability to detect even rare adverse events (Joshi *et al.*, 2002). Remifentanyl seems to have potency as an alternative to fentanyl as long as the known negative event risks can be detected and managed properly.

Most of the adverse events recorded during the use of remifentanyl have been known as part of adverse drug reactions. The clinical trial of remifentanyl has reported the following adverse drug reactions, including common adverse drug reactions, important identified risks, and important potential risks (Joshi *et al.*, 2002; Myles *et al.*, 2002). Common adverse drug reactions include bradycardia, muscle rigidity, nausea, vomiting, shivering, hypotension, nausea and vomiting, drowsiness, and dizziness. For important identified risks, remifentanyl showed cardiovascular effects such as hypotension and bradycardia, respiratory depression, drug dependence, and withdrawal syndrome. There are drug abuse/misuse and cardiac arrhythmia under important potential risks. However, another multicenter phase IV study suggested that reducing the initial dose of remifentanyl might prevent hemodynamic side effects (Joshi *et al.*, 2002).

**Table 6.** The management of adverse events.

No	Type of management	N (%)
1	Management of adverse events	
	Need for treatments	17 (40.5)
	No need for treatments	25 (59.5)
	Prolonged hospitalization	2 (4.8)
2	Use of remifentanyl	
	Stop remifentanyl	8 (19.0)
	Reduce dose of remifentanyl	17 (40.5)
3	Condition of adverse events	
	Cure without sequelae	39 (92.9)
	Cure with sequelae	3 (7.1)
4	Still ongoing	8 (19.0)
	Condition of patient	
	Cured and discharged from hospital	28 (66.7)
	Not cured and discharged from hospital	14 (33.3)
	Worsened	
		0

Though remifentanyl has potential adverse events, it has some benefits. Compared to other anesthesia drugs such as fentanyl, remifentanyl demonstrates faster clearance, can deliver a stable intraoperative course (Twersky *et al.*, 2001), and is safe for elective surgery such as a coronary artery bypass graft (Hillel *et al.*, 1999). According to a RCT in Turkey, remifentanyl can be used until the end of surgery, which benefits surgeries with high levels of stimulation or with unknown duration (Ozkose *et al.*, 2002). Furthermore, compared to fentanyl, remifentanyl has the advantage of better functional assessments (walking without being dizzy, clear thinking, concentrating, and good communication) within the first 24 hours after anesthesia based on a large RCT (Fleisher *et al.*, 2001). A systematic review also adds up that remifentanyl might be useful for patients at risk of intraoperative awareness or obstructive sleep apnea or patients with early ambulation (Komatsu *et al.*, 2007).

This study observed the range of patients from six different hospitals in Indonesia. The limitations of this study include the minimal sample sizes that do not allow subgroup analysis and the considerable short period of follow-up. The results might differ from the results in populations other than Indonesians that were included in this study.

## CONCLUSION

Based on this pharmacovigilance study, there are no additional safety concerns related to remifentanyl as an analgesic and sedative drug indicated for patients on intubation, invasive mechanical ventilation, and NIV. No evidence emerged of previously unknown side effects. Nevertheless, further study with larger patient groups considering potential subgroup analysis and a longer period of observation is needed to observe the new rare and delayed adverse drug reaction of remifentanyl.

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## CONFLICT OF INTEREST

All authors declare no conflicts of interest regarding this article.

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## ETHICAL APPROVAL

The study was held in compliance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guideline and the Declaration of Helsinki. Informed consent was obtained from all participants prior to study procedures. The protocol has been approved by the ethics committee (approval no. KE/FK/1155/EC/2017).

## DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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## AUTHOR CONTRIBUTIONS

Authors JAT, JHH, and LAC are responsible for original design, study conduct, causality assessment, data collection, data analysis, and article writing.

## DISCLOSURE

Authors NH, RKD, RP, and DJP are PT Kimia Farma Tbk employees, which funded this study. However, the funder does not have any involvement in or influence on the study outcome. The funder was not involved during the process of study, and all the investigators are independent.

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