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A Post-Marketing Study of Pethidine in Indonesia: Safety Profile

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Abstract

BACKGROUND: Pethidine, along with morphine and tramadol, is one of the frequently used drugs for post-operative pain management. It is important to ensure the product's safety and, ultimately, the safety of the patients as users of pethidine.

AIM: We aimed to investigate safety profile of Pethidine in Indonesia.

METHODS: A post-marketing surveillance study was conducted with a retrospective cross-sectional design using medical records and hospital pharmacy data in patients admitted to the inpatient or emergency department of Dr. Sardjito General Hospital, Yogyakarta, between January and December 2016. The data were analyzed descriptively to estimate the proportion of adverse events (AEs), including serious adverse events (SAEs).

RESULTS: Of the 576 patients hospitalized at the Dr. Sardjito General Hospital, 200 medical records were selected using a consecutive sampling method. A total of 120 of the 200 subjects were found to have 245 any adverse events (AEs), including serious adverse events (SAEs) following the administration of pethidine. There were 23 classifications of expected AE and 148 classifications of unexpected AE following the administration of pethidine. The duration of AE/SAE found ranged from 0 to 11 days. A total of 101 (50.5%) and 85 (42.5%) subjects experienced AE/SAE with duration <24 h and between 1 and 2 days, respectively. The most extended duration of the event was pain with 11 days. There were 23 types of expected AE/SAE from pethidine found in subjects, with the highest number of expected AE/SAE were weakness, vomiting, and dizziness of 24 (25%), 16 (16.8%), and 10 (10.5%), respectively. The expert panel team, with consideration of other concomitant medications, concluded five types of unexpected SAEs that are possible to pethidine, including respiratory acidosis, urinary tract infections, acute kidney injury, icteric, and electrolyte imbalance.

CONCLUSION: A post-marketing surveillance study provides a 50 mg/ml pethidine safety profile in Indonesia. A total of 120 of the 200 subjects who received pethidine experienced 245 adverse events (AEs) or serious adverse events (SAEs). AEs/SAEs were divided into 23 expected events and 148 types of unexpected events. According to expert panel review, few SAEs were considered possibly related to pethidine. No evidence emerged of previously unknown side effects.

Introduction

Pethidine, along with morphine and tramadol, is one of the frequently used opioid drugs for post-operative pain management. Pethidine (μ-receptor agonist) is 8–10 times less potent than morphine and has a short duration of action (between 2 and 3 h) [1]. In a randomized controlled trial, pethidine analgesic efficacy was comparable to morphine, both in reducing pain and patient satisfaction [2]. This study also indicated pethidine adverse event was relatively equal to those of morphine, with nausea and vomiting being the most common adverse effects. The other unpleasant experience was associated with smooth muscle suppressions, that is, constipation and urine retention [2].

Pethidine was approved in early 1940 as a highly effective analgesic agent [3]. Pethidine prescriptions were not restricted to as an analgesic medicine; it was also frequently used as a local anesthetic, particularly for peripheral and spinal (intrathecal) nerve blocks. Pethidine alone or in combination with other anesthetics became popular as spinal anesthesia in the early 1980s and remained so until the 20th century [4]. The pethidine short duration of anesthetic effect was beneficial for quick surgery [5].

Pethidine is an opioid medication available in oral tablet form and as a liquid injection. Microsomal enzymes metabolize this medication in the liver by two mechanisms: Hydrolysis and demethylation [6]. Hydrolysis results in the formation of meperidine, the drug's active metabolite, while demethylation results in the formation of norpethidine. Norpethidine

is frequently related to more serious adverse events such as seizures, delirium, and serotonin syndrome, as well as addiction [7]. Because pethidine is more likely to cause dependence and cognitive damage than other opioids, some countries and facilities have restricted or even removed it from their formularies, though the agent is still widely prescribed around the world [6], [8]. Furthermore, pethidine is still widely used in Indonesia, but no studies have evaluated this drug's safety profile.

It is important to ensure the product's safety and, ultimately, the patients' safety as pethidine users. Post-marketing surveillance is important to monitor the side effects of drugs and the safety profile in pethidine. Pethidine injection of 50 mg/mL is a narcotic analgesic produced and circulated in Indonesia.

Materials and Methods

A post-marketing surveillance study was conducted with a retrospective cross-sectional design using medical records and hospital pharmacy data. This study aimed to assess the safety profile of pethidine injection 50 mg/ml at the Dr. Sardjito General Hospital. The population was all patients admitted to the inpatient or emergency department of Dr. Sardjito General Hospital and obtained a pethidine injection of 50 mg/ml between January and December 2016. The exclusion criteria include the medical records that were unavailable or incomplete.

The endpoints of this study include the prevalence of all adverse events reported after administering a pethidine injection of 50 mg/ml during the patient's hospitalization. The study also collected the subjects' demographic data, history of the disease, laboratory results, and concomitant medications. This study's sample size was calculated with the assumption that 15% of subjects/patients in the population would experience at least one adverse event, resulting in a required total minimum sample size of 196 subjects.

Data were collected by the trained surveyors using an electronic case report form (CRF) that was prepared and validated by the Clinical Epidemiology and Biostatistics Unit (CEBU) Universitas Gadjah Mada (UGM)/Dr. Sardjito General Hospital, as the data management center of the study. CRF data have been verified by 10% to ensure the quality of the data collection. The monitoring team carried out verification. The causality analysis of AE/SAE was identified by a team panel of experts consisting of a pharmacologist, specialist doctor, epidemiologist, and pharmacist using Naranjo's scores. Each expert assessed individually and independently then discussed whenever differences were found. Variables with categorical data were described as numbers and percentages, and variables with continuous data were expressed as mean and min-max.

AE/SAE was categorized into primary and secondary system organ classes (SOCs) using Medical Dictionary for Regulatory Activities (MedDRA®) System. The expected and unexpected AEs/SAEs were assessed with the Naranjo score, where AE/SAE with Naranjo score ≥ 1 is further discussed in an expert panel to discuss the unexpected findings. The panel examined whether SAE's findings constitute possible adverse events caused by the administration of pethidine or fall into the warning category in pethidine users.

Before the data collection is carried out, this research protocol has been submitted to get ethical clearance from the Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada. The research permit was obtained from Dr. Sardjito General Hospital, while the training for surveyors in CRF completion has been done before data collection.

Results

Baseline characteristics

A total of 576 patients received pethidine while undergoing hospitalization during 2016 at Dr. Sardjito General Hospital. Of the 576 patients, 200 patients' medical records were selected using the consecutive sampling method from January to March 2018. The demographic characteristics of the subjects are presented in Table 1. The high number of subjects receiving pethidine was between 35 and 49 years of age, with 47 (23.5%). Two-thirds of subjects receiving pethidine used government insurance with 155 (77.5%). There were 24 (12%) fully recovered and 14 (7%) died. Most subjects receiving pethidine were undergoing surgery with 186 (93%).

Table 1: Baseline characteristics of the subjects

Characteristic	Number (%)
Sex	
Male	89 (44.5)
Female	111 (55.5)
Age category	
0−14 years	8 (4)
15−24 years	44 (22)
25−34 years	46 (23)
35−49 years	47 (23.5)
50−64 years old	28 (14)
> 64 years old	27 (13.5)
Type of insurance (%)	
Non-insurance	44 (22)
Government insurance (*Jaminan Kesehatan Nasional/JKN*)	155 (77.5)
Private insurance	1 (0.5)
Outcomes (%)	
Fully recovered	24 (12)
Recovered with sequelae	1 (0.5)
Death	14 (7)
Others	161 (80.5)
Number of subjects receiving concomitant medications	200 (100)
Number of subjects undergoing surgery	186 (93)

Other medications used during treatment

All subjects receiving pethidine also received at least one type of concomitant medication during treatment/hospitalization at the Dr. Sardjito General Hospital. The 20 most common types of concomitant medications received by subjects are presented in Table 2. Of 200, there were patients who obtained anesthetic drugs, such as fentanyl in 133 (66.5%) and propofol in 95 (47.5%), and sevoflurane in 71 (30.5%) patients during the study. The list of all types of concomitant medications received is described in Supplementary Table S1-S3.

Table 2: The most common types of concomitant medications received by subjects

ATC code	Name of the drug	Number of patients (%)
V03AN01	Oxygen	186 (93.0)
M01AB15	Ketorolac	164 (82.0)
A04AA01	Ondansetron	158 (79.0)
B05BB01	Ringer lactate	140 (70.0)
N01AH01	Fentanyl	133 (66.5)
B05BB01	Electrolyte	127 (63.5)
B05XA03	Normal saline	114 (57.0)
A02BA02	Ranitidine	110 (55.0)
J01DD04	Ceftriaxone	103 (51.5)
N05CD08	Midazolam	101 (50.5)
N01AX10	Propofol	95 (47.5)
N01BB01	Bupivacaine	73 (36.5)
N01AB08	Sevoflurane	71 (30.5)
N02BE01	Paracetamol	68 (34.0)
R07AX01	Nitric oxide	68 (34.0)
J01DD01	Cefotaxime	64 (32.0)
M03AC09	Rocuronium	63 (31.5)
B02AA02	Tranexamic acid	60 (30.0)
M01AG01	Mefenamic acid	58 (29.0)
B05AX01	Packed red cell transfusion	47 (23.5)

Laboratory examination

A total of 130 subjects (60%) had at least one abnormal laboratory result following the administration of pethidine (Table 3).

Table 3: Abnormal laboratory results after obtaining pethidine

Code	Type of examination	Unit	Number of subjects	(min, max)
A. Hematology and coagulation				
1	Erythrocyte count	$x10^6/mm^3$	56	(2.26, 78.9)
2	Hemoglobin	g/dL	41	(7, 13.9)
3	Mean corpuscular volume (MCV)	Fl	10	(73.4, 99.8)
4	Mean corpuscular hemoglobin (MCH)	Pg	9	(23.3, 79.7)
5	Mean corpuscular hemoglobin concentration (MCHC)	g/dL	9	(30.1, 36.4)
6	Red cell distribution width (RDW)	%	28	(11.4, 46.8)
7	Leukocyte count	$x10^3/mm^3$	56	(3.38, 27.65)
8	Leukocyte differential count			
a.	Basophil	%	2	(0, 0.01)
b.	Eosinophil	%	78	(0, 5.9)
c.	Rod neutrophil	%	2	(0.1,0.1)
d.	Neutrophils	%	74	(12.8, 97.6)
e.	Lymphocytes	%	70	(1, 95.5)
f.	Monocyte	%	26	(0.3, 18.1)
9	Platelet count	$x10^3/mm^3$	21	(45, 926)
10	Prothrombin time (PT)	seconds	15	(10.9, 43.1)
11	Activated partial thromboplastin time (APTT)	seconds	10	(18.4, 94.5)
B. Kidney function				
1	Creatinine	ng/mL	6	(0.47, 7.23)
2	Blood urea nitrogen (BUN)	mg/dL	10	(4.4, 83.1)
C. Electrolytes				
1	Sodium	mEq/L	8	(127, 147)
2	Potassium	mEq/L	8	(2.81, 6.4)
3	Calcium	mg/dL	2	(1.72, 3.2)
4	Chloride	mEq/L	11	(96, 114)
5	Magnesium	mg/dL	2	(1.3, 1.54)
D. Hepatobiliary				
1	Alanine aminotransferase (ALT)	U/L	3	(44, 134)
2	Aspartate aminotransferase (AST)	U/L	6	(42, 71)
3	Albumin	g/dL	18	(2.21, 3.96)
E. Lipid profile				
1	Total cholesterol	mg/dL	2	(207, 209)
2	Triglycerides	mg/dL	2	(156, 185)
3	Low-density lipoprotein (LDL)	mg/dL	4	(119, 134)
4	High-density lipoprotein (HDL)	mg/dL	4	(25, 39)
F. Blood sugar				
1	Blood glucose when	mg/dL	5	(56, 196)
2	Fasting blood glucose	mg/dL	3	(111, 212)
4	HbA1c	%	1	(8.1, 8.1)

Adverse event (AE) and serious adverse event (SAE)

A total of 120 (60%) of the 200 subjects were found to have at least one AE (serious and non-serious) following the administration of pethidine. The total AE/SAE recorded was 245, with the event numbers ranging from 1 to 10 events occurring per subject. A total of 66 (33%) subjects experienced only one type of AE/SAE, while only one subject experienced 10 types of AE/SAE (Table 4).

The duration of AE/SAE found ranged from 0 to 11 days. A total of 101 (50.5%) and 85 (42.5%) subjects experienced AE/SAE with a duration below 1 day and between 1 and 2 days, respectively. The longest duration of the event was pain, with a duration of 11 days. The list of durations of AE/SAE experienced by the patient is presented in Supplementary Table S1. The AE/SAE classification showed that 245 AEs/SAEs were classified in 17 primary SOCs, while 116 AEs/SAEs were classified in 12 secondary SOCs (Table 5).

AE/SAE was classified into expected and unexpected events. There were 23 types of expected AE/SAE from pethidine found in subjects, with the highest number of expected AE/SAE which were weakness, vomiting, and dizziness of 24 (25%), 16 (16.8%), and 10 (10.5%), respectively (Supplementary Table S2). There were 148 unexpected AE/SAE classified into 54 types of AE/SAE (Supplementary Table S3). The most experienced unexpected AE was pain (35 events) and post-operative pain (18 events). Conclusions from expert panel discussions are described in Table 6.

Table 4: Frequency of AE/SAE experienced by the subject

Number of AE/SAE	Number of subjects (%)
1	66 (33)
2	25 (12.5)
3	12 (6.0)
4	7 (3.5)
5	3 (1.5)
6	3 (1.5)
7	2 (1.0)
8	1 (0.5)
10	1 (0.5)
Total	120 (60)

Discussion

This study suggested the adverse events, including the serious adverse events found after using 50 mg/ml pethidine in patients hospitalized at the Dr. Sardjito General Hospital, 60% of the patients. The unexpected SAE was evaluated by an expert panel using

Table 5: System organ classes (SOCs) for AE/SAE found

SOC code	TERM SOC	Number of events (%)
Primary SOCs		
10018065	General disorders and administration site conditions	73 (29.8)
10017947	Gastrointestinal disorders	36 (14.7)
10028395	Musculoskeletal and connective tissue disorders	28 (11.4)
10029205	Nervous system disorders	22 (8.9)
10038738	Respiratory, thoracic, and mediastinal disorders	22 (8.9)
10038359	Renal and urinary disorders	17 (6.9)
10007541	Cardiac disorders	11 (4.5)
10027433	Metabolism and nutrition disorders	6 (2.4)
10021881	Infections and infestations	5 (2.0)
10040785	Skin and subcutaneous tissue disorders	5 (2.0)
10047065	Vascular disorders	5 (2.0)
10019805	Hepatobiliary disorders	4 (1.6)
10037175	Psychiatric disorders	4 (1.6)
10005329	Blood and lymphatic system disorders	3 (1.2)
10015919	Eye disorders	2 (0.8)
10014698	Endocrine disorders	1 (0.4)
10036585	Pregnancy, puerperium, and perinatal conditions	1 (0.4)
Total		245 (100.00)
Secondary SOCs		
10018065	General disorders and administration site conditions	28 (11.4)
10022117	Injury, poisoning and procedural complications	22 (8.9)
10047065	Vascular disorders	13 (5.3)
10021881	Infections and infestations	12 (4.9)
10027433	Metabolism and nutrition disorders	12 (4.9)
10007541	Cardiac disorders	11 (4.5)
10037175	Psychiatric disorders	6 (2.4)
10038738	Respiratory, thoracic, and mediastinal disorders	4 (1.6)
10021428	Immune system disorders	3 (1.2)
10005329	Blood and lymphatic system disorders	2 (0.8)
10029205	Nervous system disorders	2 (0.8)
10038604	Reproductive system and breast disorders	1 (0.4)
AE with secondary SOCs		116 (47.3)
AE without secondary SOCs		129 (52.7)
Total		245 (100.00)

the Naranjo Adverse Drug Reaction Probability Scale (Naranjo scale). Naranjo scale was developed to predict the probability that a drug administered in therapeutic doses caused an adverse event, thereby classifying the event as an adverse drug reaction (ADR). Naranjo scale is also evaluated if there are alternative causes (concomitant drug or other than the drug) that could be associated with the event [9]. Several unexpected SAEs were found to be a Naranjo score ≥ 1, categorized as a possible adverse event. Some common possible adverse events following the administration of pethidine include acute kidney injury, icteric, electrolyte rewards, respiratory acidosis, and urinary tract infections. Most adverse events might likely be caused by pethidine atropine-like effects, including dry mouth and blurred visions [1], or by pethidine serotonin reuptake inhibition effects [10]. All the adverse event types were considered similar to previous safety profiles of pethidine indicated by the Food and Drug Administration (FDA) and other safety studies [7], [10], [11], [12]. There is no additional safety concern, according to this study's findings.

Table 6: Naranjo scores for each unexpected SAE assessed by the expert panel

Serious adverse event	Naranjo score	Category
Acute kidney injury	3	Possible
Icteric	3	Possible
Electrolyte imbalance	2	Possible
Respiratory acidosis	2	Possible
Urinary tract infection	2	Possible

Score description: 1–4=Possible 5–8=Probable, >8=Definitely/highly probable.

Pethidine has been officially identified by the Food and Drug Administration (FDA) to have urinary retention, biliary tract spasm, and reduced pancreatic secretion adverse events. Urinary retention may result in urinary tract infection and acute kidney injury, while biliary spasm may result in icteric occurrence. Although all opioids increase biliary tract pressure, a study found that meperidine increased the risk of bile duct pressure compared to morphine in patients undergoing cholecystectomy [10], [13]. This study suggested respiratory acidosis and electrolyte imbalance as possible adverse events of pethidine. The FDA reported that pethidine could affect respiratory depression [11], which may theoretically lead to respiratory acidosis. Furthermore, the adverse events of respiratory or cardiac disorders might also be attributed to concomitant anesthetic drugs such as fentanyl, propofol, and sevoflurane. A previous double-blind, randomized cross-over trial of pethidine and tramadol suggested that pethidine does not clinically change either in SpO2 or in hemodynamic [14].

The age range of patients experiencing adverse events was between 3 and 87 years old, with 77% over 38 years. A longitudinal study of pethidine prescribing in older adults suggested that older adults may experience more adverse events due to sensitivity to the central nervous system and reduced renal functions due to aging [8], [12]. However, pethidine has some benefits out of its ultimate indication of the analgesic agent. Based on several studies, pethidine is more effective in controlling post-operative shivering than fentanyl or other similar drugs [15], [16], [17]. Pethidine with a dose of 25 or 50 mg is appropriate for post-operative shivering [10]. Furthermore, a double-blind, randomized controlled trial with 103 patients suggested that there is no difference between morphine and pethidine in the efficacy, side effect, and patient satisfaction for analgesia [2].

In this study, all subjects received concomitant medications. Of the 20 most common types of concomitant medications, several drugs were associated with pethidine. Types of drugs and symptoms of these interactions found include fentanyl (sedation, respiratory depression, coma, death, and hypotension), ondansetron (symptoms of serotonin syndrome, autonomic dysfunction neuromuscular disorders, and gastrointestinal disorders), midazolam (respiratory depression, hypotension, sedation, fainting, coma, and death, especially in the elderly), propofol (central nervous system and cardiorespiratory system depression), and bupivacaine (increases the risk of local anesthetic drug toxicity) [18].

A safety study in the U.S. suggested that adverse events of meperidine (pethidine) were associated with concomitant benzodiazepine [8]. However, in this study, there is no concomitant benzodiazepine administration with pethidine included. The expert panel team, with consideration of other concomitant medications being used, concluded five types of unexpected SAEs that are possible to pethidine, including respiratory acidosis, urinary tract infections, acute kidney injury, icteric, and electrolyte imbalance.

The strength of this study is the number of subjects and independent expert panels to assess the study's endpoint. However, due to the nature of one arm post-marketing surveillance, this study did not analyze or compare to control or other drugs. Furthermore, the

weakness of this study is a retrospective study design which may result in reporting bias.

Conclusion

A post-marketing surveillance study provides a 50 mg/ml pethidine safety profile in Indonesia. A total of 120 of the 200 subjects who received pethidine experienced 245 adverse events (AEs) or serious adverse events (SAEs). AEs/SAEs were divided into 23 expected events and 148 types of unexpected events. According to expert panel review, few SAEs were considered possibly related to pethidine. No evidence emerged of previously unknown side effects.

Acknowledgment

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Consent of Ethics

The study was held in compliance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guideline and Declaration of Helsinki. Informed consent was obtained from all participants before study procedures. The protocol has been approved by the local ethics committee.

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Supplementary Material

Table S1: Duration of AE/SAE

No	AE/SAE	Duration of AE/SAE				Total
		0 days	1-2 days	3-4 days	5-11 days	
1	Radial Abscess	0	0	1	0	1
2	Acute Kidney Injury	1	0	0	1	2
3	Anemia	1	1	1	0	3
4	Metabolic Acidosis	2	0	0	0	2
5	Respiratory Acidosis	1	0	0	0	1
6	Cough	3	2	0	0	5
7	Eye Spot	1	0	0	0	1
8	Skin Spot	1	0	0	0	1
9	Bradycardia	3	0	0	0	3
10	Cerebral Concussion	0	1	0	0	1
11	Fever	2	1	0	0	3
12	Rheumatic Fever	1	0	0	0	1
13	Diarrhea	0	1	0	0	1
14	Dyspepsia	1	1	0	1	3
15	Cervical Dystonia	0	0	1	0	1
16	Edema	4	6	0	0	10
17	Pulmonary Edema	2	1	0	0	3
18	Pleural Effusion	0	1	0	1	2
19	Embolism	1	0	0	0	1
20	Epistaxis	0	1	0	0	1
21	Itchiness	1	2	0	1	4
22	Restless	4	0	0	0	4
23	Tremble	1	0	0	0	1
24	Hematuria	1	2	0	0	3
25	Hemiparesis	0	0	1	0	1
26	Hyperkalemia	0	0	1	0	1
27	Hypertension	1	0	1	0	2
28	Hyperthermia	1	0	0	0	1
29	Hypoalbuminemia	0	1	0	1	2
30	Hypotension	1	0	0	0	1
31	Hypothermia	0	1	0	0	1
32	Icteric	2	0	0	0	2
33	Electrolyte Imbalance	0	1	0	0	1
34	Urinary Tract Infection	2	5	0	2	9
35	Cardiomegaly	1	0	0	0	1
36	Bloating	2	2	0	0	4
37	Tissue Disintegration	0	0	1	0	1
38	Constipation	0	1	0	0	1
39	Contraction	0	1	0	0	1
40	Cramp	1	0	0	0	1
41	Weak	11	9	3	1	24
42	Sleepiness	4	1	0	0	5
43	Nausea	1	0	0	0	1
44	Dry Mouth	1	0	0	0	1
45	Vomiting	12	4	0	0	16
46	Reduced Appetite	1	0	0	0	1
47	Pain	2	13	11	9	35
48	Chest Pain	2	0	0	0	2
49	Headache	1	1	0	0	2
50	Abdominal Pain	2	0	0	2	4
51	Postoperative Pain	2	6	8	2	18
52	Jaw Pain	0	0	1	0	1
53	Hand Pain	1	0	0	0	1
54	Swallow Pain	0	1	0	0	1
55	Neck Pain	0	1	0	0	1
56	Heartburn	3	0	0	0	3
57	Palpitations	0	1	0	0	1
58	Syncope	1	0	0	0	1
59	Pneumonia	1	1	0	1	3
60	Pulsating Mass	0	1	0	0	1
61	Dizziness	5	4	1	0	10
62	Sepsis	1	2	0	0	3
63	Dyspnea	4	5	1	0	10
64	Cyanosis	1	0	0	0	1
65	Systemic Inflammatory Response Syndrome	0	1	0	0	1
66	Stress Ulcer	0	1	0	0	1
67	Speech Difficulty	1	0	0	0	1
68	Dysuria	0	0	1	0	1
69	Kidney Trauma	0	0	0	1	1
70	Traumatic Optic Neuropathy	0	1	0	0	1
71	Tuberculosis	1	0	0	0	1
72	Concentrated Urine	1	0	0	0	1
	Total	101	85	33	23	242

Table S2: Expected AE/SAE from pethidine experienced by subjects

No.	Expected AE	Number of events	% of total events
1	Weakness	24	24.7%
2	Vomiting	16	16.5%
3	Dizziness	10	10.3%
4	Dyspnea	9	9.3%
5	Itchiness	4	4.1%
6	Restlessness/Agitation	4	4.1%
7	Drowsiness/Delirium	4	4.1%
8	Abdominal Pain/Constipation	4	4.1%
9	Bradycardia	3	3.1%
10	Shaking/Tremor	2	2.1%
11	Hypertension	2	2.1%
12	Chest Pain	2	2.1%
13	Skin Spots	1	1.0%
14	Hyperthermia	1	1.0%
15	Hypotension	1	1.0%
16	Constipation	1	1.0%
17	Nausea	1	1.0%
18	Dry Mouth	1	1.0%
19	Headache	1	1.0%
20	Palpitations	1	1.0%
21	Faint	1	1.0%
22	Dysuria	1	1.0%
23	Concentrated Urine	1	1.0%
	Total	97	100.0%

Table S3: Unexpected AE/SAE from pethidine experienced by subjects

No	Unexpected AE/SAE	Number of events	% of total events
1	Pain	35	23.6%
2	Postoperative pain	18	12.2%
3	Urinary tract infection	9	6.1%
4	Edema	8	5.4%
5	Cough	5	3.4%
6	Bloating	4	2.7%
7	Anemia	3	2.0%
8	Fever	3	2.0%
9	Dyspepsia	3	2.0%
10	Pulmonary Edema	3	2.0%
11	Hematuria	3	2.0%
12	Heartburn	3	2.0%
13	Pneumonia	3	2.0%
14	Sepsis	3	2.0%
15	Acute kidney injury	2	1.4%
16	Metabolic acidosis	2	1.4%
17	Pleural effusion	2	1.4%
18	Hypoalbuminemia	2	1.4%
19	Icteric	2	1.4%
20	Systemic inflammatory response syndrome	1	0.7%
21	Radial abscess	1	0.7%
22	Respiratory acidosis	1	0.7%
23	Black spots of the eyes	1	0.7%
24	Cerebral concussion	1	0.7%
25	Rheumatic fever	1	0.7%
26	Diarrhea	1	0.7%
27	Cervical dystonia	1	0.7%
28	Embolism	1	0.7%
29	Epistaxis	1	0.7%
30	Graves' disease	1	0.7%
31	Hemiparesis	1	0.7%
32	Hyperkalemia	1	0.7%
33	Hypothermia	1	0.7%
34	Electrolyte imbalance	1	0.7%
35	Cardiomegaly	1	0.7%
36	Damage to network integrity	1	0.7%
37	Contraction	1	0.7%
38	Cramp	1	0.7%
39	Sleepiness	1	0.7%
40	Reduced appetite	1	0.7%
41	Headache	1	0.7%
42	Jaw pain	1	0.7%
43	Hand pain	1	0.7%
44	Swallow pain	1	0.7%
45	Neck pain	1	0.7%
46	Pulsating mass	1	0.7%
47	Cyanosis	1	0.7%
48	Stress ulcer	1	0.7%
49	Difficulty communicating	1	0.7%
50	Kidney trauma	1	0.7%
51	Traumatic optic neuropathy	1	0.7%
52	Tuberculosis	1	0.7%
	Total	148	100.0%