Off-label use of pentazocine and the associated adverse events among pediatric surgical patients in a tertiary hospital in Northern Nigeria: a retrospective chart review

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ABSTRACT
Background and aims: Pentazocine remains a widely used opioid pre-anesthetic medication and post-operative analgesic in low- and middle-income countries (LMICs) despite concerns. We assessed the adverse events (AEs) associated with off-label use of pentazocine in pediatric surgical patients and determined the possible risk factors associated with slow respiratory AEs. **Method**: Children ≤ 18 years old for surgery administered pentazocine IM/IV as a pre-anesthetic medication or post-operative analgesic. Pertinent data including total daily dose and duration of use of pentazocine and its associated AEs were obtained from patients' case files. Risk factors associated with slow respiratory AEs were determined using logistic regression analyses. **Results**: 159 patients were included with median age of 2 years and mainly males (52.8%). Pentazocine was administered off-label to all patients for post-operative pain management (96.2%) or pre-anesthetic medication (3.8%). All patients experienced at least one AE with most experiencing 2-7 AEs. Rapid breathing (116; 18.4%), followed by sleepiness/sedation/drowsiness (90; 14.3%) and fast pulse (79; 12.5%) was the most frequently reported AEs. None of the demographics and clinical variables significantly predicted the risk of slow respiratory AEs. **Conclusion**: Off-label use of pentazocine is common and associated with multiple AEs. Care is needed as no predictors of slow respiratory AEs were observed.

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1. Introduction

A considerable number of the prescription medicines commonly used among children lack information in the product labeling regarding their safety, efficacy and dosing [1]. As a result, many medicines are used off-label in children [2, 3]. Off-label and unlicensed medicines use for children now requires a legal obligation for the physician to adequately inform the patients or their caregivers on the benefits and risks of such medicines, which may require an informed consent before prescribed [4].

Antimicrobial agents and analgesics (opioid and non-opioid) are two important classes of medicines often prescribed off-label for children [5], with safety aspects associated with analgesic medicines a concern. A systematic review of randomized controlled studies of opioid use post-operatively or for trauma pain in pediatric patients reported a significant respiratory depression in one of the studies [6]. Other studies have reported both severe respiratory depression and deaths in children following post-operative use of opioid analgesics [7, 8]. Previous studies evaluating adverse events (AEs) associated with off-label medicine use in children have defined the term "adverse event" as "any untoward event associated with the use of a medicine in humans, whether or not considered medicine related" [9].

Pentazocine was the first opioid agonist-antagonist to be used in clinical practice as an analgesic in the United States in 1967 [10], and remains one of the most widely used opioid pre-anesthetic medications and post-operative analgesics in low-income and middle-income countries (LMICs) despite lack of pediatric labeling globally [10, 11]. For instance, a survey of post-operative pain management among pediatric surgeons in Nigeria found that out of the 43 surgeons interviewed, 32% would recommend pentazocine for neonates, while 80% would recommend pentazocine for older children [12]. Due to continuing unmet need for analgesics in pediatric pain management, the United States has required studies to evaluate the safety of analgesics used in children [13]. However, only a few studies have been

completed to date leading to their limited approval and license for pediatric use [13, 14]. Consequently, pentazocine and many other opioid and non-opioid analgesics are used off-label among pediatric patients.

Following the abuse of pentazocine and its addiction in the United States in 1972, it was discontinued and later remarketed as pentazocine- acetaminophen and pentazocine- naloxone fixed combinations [15]. Prior to its discontinuation, pentazocine was used off-label to manage severe pain in children that may require an opioid analgesic and for which alternative treatments are inadequate [16]. Pentazocine was also used as a pre-operative or pre-anesthetic medication and as a supplement to surgical anesthesia in children. The pediatric dosing for analgesia was based on the limited pharmacokinetic and pharmacodynamics data from earlier studies in children [17, 18] coupled with the safety data reported from a few clinical trial studies in children [19, 20]. In the 1970s, children ≥ 1 year old were recommended 0.5 mg/kg IM/IV single dose pentazocine as a pre-operative or pre-anesthetic medication, while children 5-8 years were recommended pentazocine 15 mg IM/IV, every 6-8 hours; and those ≥ 9 years received 30 mg IM/IV, every 6-8 hours, as analgesics [14, 17]. It is very likely that the current dosing regimen of pentazocine in resource-limited countries is still based on the safety data published earlier in high-income countries. To date no pharmacokinetic studies and safety data have emerged from LMICs to guide rational use of pentazocine for children. This is important given the potential AEs in children.

There are several AEs associated with pentazocine use in both adults and children. The common AEs include nausea and vomiting, while cough, difficulty in breathing, fever, itching, and diarrhea are rare [10, 11, 14]. However, serious, life-threatening, or fatal respiratory depression may occur with pentazocine use in children [8, 10]. Consequently, it is important to monitor for respiratory depression during initiation of pentazocine or following a dose increase. A study evaluating the post-operative AEs of pentazocine among 49 surgical neonates in Nigeria reported 40 patients with respiratory depression; of which 15 resulted in death, 46 patients with over-sedation, and 45 patients with recurrent apnea [8]. Among 60 pediatric patients who received 0.5mg/kg pentazocine for adenotonsillectomy, four developed marked apprehension following pre-anesthetic induction [21].

Although rare AEs to pentazocine have not been reported in children, myofibrosis and its calcified form had been reported in adults following prolonged use of high-dose pentazocine [22, 23]. Other rare AEs reported in adults include fibrosis at the injection site [24], irregular punched-out abscesses with a rim of hyper-pigmentation surrounding the ulcer [25, 26], bilateral deep vein thrombosis, toxic epidermal necrolysis, generalized erythematous desquamative rash [27], fibromyositis and contracture [28].

Consequently, we sought to evaluate the off-label use of pentazocine among pediatric surgical patients in a Northern teaching hospital in Nigeria, and to report the associated AEs to aid our understanding while building on earlier studies in Nigeria. Whilst Osifo *et al* evaluated the AEs of pentazocine among pediatric surgical patients in Nigeria; their focus was on neonates experiencing respiratory depression or death related problems [8]. This study was also conducted 10 years ago and did not specify the ages of the children. Another limitation of their study was the inability to predict risk for the AEs, particularly respiratory depression. As a result, we also sought to identify any potential risk factors for slow or reduced respiratory rate AEs to guide future treatment decisions given concerns with pentazocine, as we believe this has not been studied before in LMICs.

2. Methods

2.1 Study Design

Most hospitals in Nigeria do not operate Electronic Medical Record system; therefore, this study was performed using the paper case files of children who had surgeries at the Usmanu Danfodiyo University Teaching Hospital, Sokoto in Northern Nigeria, from 1st January 2015 to 31st December 2017. This hospital was chosen as, it is one of the leading teaching hospitals treating children in Northern Nigeria; consequently, likely to have a number of children prescribed pentazocine pre- and post-surgery. Initially, the pediatric surgery register at the theater of the hospital was reviewed to identify potentially eligible patients. The registration number of each patient was obtained and used to retrieve each paper case file from the medical records office. The Ethics and Research Committee of the institution approved the study.

Two designated investigators (IAO and CA) from the hospital performed a retrospective chart review of the in-patients by searching their case files to identify individuals meeting the following inclusion criteria: had emergency or elective surgery, ≤ 18 years old at the time of admission for surgery, administered pentazocine IM/IV as a pre-anesthetic medication or as a post-operative analgesic. Exclusion criteria were insufficient data to determine exposure(s) or outcome and patients whose case files could not be retrieved.

2.2 Sample Size Determination

The sample size was a convenience sample and determined by the number of patients consecutively selected that met the study inclusion criteria.

2.3 Case Definition and Identification

Due to lack of information guiding the pediatric use of pentazocine in the British National Formulary for children (BNFC), 2018; the Standard Treatment Guidelines of Nigeria (STGN), and the World Health Organization Model List of Essential Medicines for Children (WHO- EMLc), 2017 [29-31], we consider its use as off-label in this study. Off-label use of any medicine in children refers to any use outside the recommended age [9].

At our center, AEs of pentazocine are routinely monitored in children by healthcare providers (surgeons and nurses) and documented in the patients' case notes over the period of treatment. As a retrospective study, no causality assessment was performed to establish the relationship between the AEs and pentazocine. Among the important AEs monitored were respiratory rate (to identify suspected tachypnea, respiratory depression or apnea), pulse rate (to identify suspected tachycardia or bradycardia), body temperature (to identify fever or hypothermia), behavioral changes (to identify irritability or apprehension), nausea and vomiting, and other AEs in pentazocine label [10] or those observed but not included in the drug label (rare AEs). The vital signs (respiratory rate, pulse rate, and body temperature) were recorded for all the patients, before and immediately after surgery, and after the patients were exposed to first dose or subsequent doses of pentazocine. Tachypnea defines an increased respiratory rate i.e., > 60 breaths/minute in children < 2 months old, > 50 breaths/minute in children 2-12 months old, and >40 breaths/minute in children >1 year old [32]. Respiratory rates lower than those defined for the age were considered as respiratory depression or apnea if the respiration ceases for ≥20 seconds with or without bradycardia or cyanosis [33]. Sinus tachycardia defines an increased pulse or heart rate i.e., > 230 beats/minute in neonates, >170 beats/minute in infants, >120 beats/minute in toddlers and young children, and >100 beats/minute in older children and adolescents [34]. On the other hand, bradycardia defines a decreased pulse or heart rate below the normal range for age (i.e., <100 beats/minute for infants, <80 beats/minute for toddlers and young children, <70 for older children, and <60 for adolescents) [35].

Surgeries were classified as major and minor according to previous studies [36, 37]. Major surgery is any invasive operative procedure in which a more extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered. The recovery time can be lengthy and may involve a stay in intensive care or several days in the hospital. Minor surgery is any invasive operative procedure in which only skin or mucus membranes and connective tissue is resected e.g. incisional or excisional biopsy, repair of hernia, and removal of skin lesions. The recovery time is short and patient usually returns to their usual activities rapidly.

2.4 Primary Outcome and potential confounders

The primary outcome of interest was presence or absence of any AEs, which included clinically, diagnosed AEs (those reported by the patient or their parent/guardian to healthcare providers, or those discovered by surgeons or nurses after physical examination and entered into the patient's notes) immediately or not later than a week after exposure to first dose or subsequent doses of pentazocine. The one-week time frame to detect AEs was based on a 72-hour maximum duration of exposure to pentazocine among pediatric age groups previously evaluated for post-operative pain management in Nigeria [8]. Investigators manually reviewed the paper case file of each patient and extracted the relevant data using a self-designed pro forma. AEs were defined as any untoward medicine experience occurring

at any dose following pentazocine administration, which may or may not be solely related to the medicine. The AEs are considered severe if they resulted in death, a life-threatening condition, hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, or other event requiring intervention [9]. For this study, investigators determined the incidence of these outcomes following IM/IV administration of pentazocine.

Potential confounders for the primary outcome were determined *a priori* and collected through manual review of the case files. These variables included demographic data (age and gender), clinical data (weight and type of surgery), and drug exposure data (total daily dose, frequency of exposure, and duration of drug use). Routinely, cefuroxime and metronidazole were used prophylactically for the pediatric surgical patients. These are often commenced in emergency patients before surgery and continued after surgery with an open duration of use, while for elective patients; antibiotics are commenced on the day of the surgery or immediately after the surgery for at least five days, although we are aware that others have recommended antibiotics prior to surgery for certain situations or no prophylactic antibiotics at all [38]. However, cefotaxime or ceftriaxone are occasionally used in place of cefuroxime in emergency patients presenting with severe sepsis or surgical complications. Consequently, concomitant medications (principally prophylactic antibiotics) were excluded from this study since they were not considered confounders because they have been rarely associated with similar AEs to pentazocine [39].

2.5 Statistical Analysis

Demographic, clinical, and dosage regimen data were described as frequencies and percentages for categorical variables or median and range for continuous variables, unless otherwise specified. Comparisons of patients with and without AE were made using Pearson Chi-square, Fisher's exact test or Mann-Whitney Test. Regarding specific AEs such as increased or decreased respiratory or pulse rates, pre-medication and immediate post-medication mean data were compared using student-paired *t*-test. Multivariate logistic regression was performed with slow or decreased respiratory rate AE as the primary outcome and the type of surgery, gender, age at commencement of pentazocine, weight at commencement of pentazocine, total daily dose of pentazocine administered, frequency of administration, and duration of use of the medicine as covariates. Data were analyzed using IBM SPSS statistics software, Version 21.0. Armonk, NY, USA: IBM. Corp (Released 2012). All p-values < 0.05 were considered to be statistically significant.

3. Results

During the 3-year study period, 164 children received pentazocine. In all, five children were excluded because the dose, dosing frequency, or duration of use of pentazocine was not documented (3) or the case files were irretrievable (2). The remaining 159 children with complete data were included in the study. They received pentazocine either for post-operative pain management (153; 96.2%) or as a pre-anesthetic medication (6; 3.8%). More male (84; 52.8%) than female (75; 47.2%) patients received pentazocine, while the median patient age was 2 years (range: 2 days-15 years) and the median weight was 10 kg (range: 2.6-35 kg).

The surgical procedures performed on the patients necessitating the use of pentazocine are shown in Figure 1. The most common were exploratory laparotomy (91; 57.2%) and appendectomy (11; 6.9%). Six children received a single dose of pentazocine (median: 13 mg, range: 12-15 mg) as a pre-anesthetic medication, while the remaining 153 children received multiple doses of pentazocine for post-operative pain management. The median daily dose received by the children as post-operative analgesic was 32 mg (range: 2-225 mg).

Pentazocine was administered off-label to all the patients. They all experienced at least one of the identified 13 AEs. The specific AEs experienced per patient are presented in Table 1. Most patients experienced between 2 and 7 AEs with those experiencing four AEs being the highest. Altogether, the 159 patients experienced 631 AEs. Rapid breathing (116; 18.4%), followed by sleepiness/sedation/drowsiness (90; 14.3%) and fast pulse (79; 12.5%) was the most frequently reported AEs (Table 1). For those patients who experienced rapid breathing, the mean respiratory rate in

breathes/minute significantly increased shortly after receiving the first dose of pentazocine compared to the rate before surgery (37.7± 8.0 vs. 32.0± 8.4, p< 0.001). Those who experienced slow breathing had their mean respiratory rate in breathes/minute significantly reduced shortly after receiving the first dose of pentazocine compared to the rate before surgery (31.1± 7.9 vs. 38.9± 9.9, p< 0.001). For those patients who experienced fast pulse rate, the mean pulse rate in beats/minute significantly increased immediately after receiving the first dose of pentazocine compared to the rate before surgery (110.7± 17.9 vs. 132.5 ± 19.8, p< 0.001).

Regarding those who experienced a slow pulse rate, the mean pulse rate in beats/minute significantly decreased immediately after receiving the first dose of pentazocine compared to the rate before surgery (121.5 ± 18.8 vs. 102.4 ± 16.5, p< 0.001). Of the 116 patients with rapid breathing and 43 patients with slow breathing, 75 (64.7%) and 27 (62.8%), respectively, responded to intranasal oxygen therapy and conservative management, while the rest recovered spontaneously to conservative management only. None of the patients experienced severe or life-threatening respiratory depression.

In multivariate analysis of the association between the demographic and clinical variables and slow respiratory AEs, after adjusting for the 7 identified covariates (type of surgery, gender, age at commencement of pentazocine, weight at commencement of pentazocine, total daily dose of pentazocine administered, frequency and duration of use of pentazocine), none of the variables was significantly associated with the AEs (Table 2).

4. Discussion

More children received pentazocine for post-operative pain management than for pre-anesthetic medication. This is in keeping with previous studies documenting pentazocine as the commonest opioid analgesic used post-operatively in children and the most frequently prescribed for post-operative pain by pediatric surgeons and resident doctors in Nigeria [8, 12]. As mentioned, there is no information guiding the prescribing of pentazocine for children in the BNFC, STGN, and WHO EMLc [29-31]; consequently, pentazocine was used off-label in our cohort. It is very likely that the surgeon's prescription was based on the dosing regimen and safety information for pentazocine published in the literature before it was discontinued in the United States [14, 15]. Furthermore, the choice of pentazocine may have been influenced by the type of surgery (minor or major) performed on the patients, the organ-system involved, the clinical state of the patients, surgeons' familiarity with pentazocine, and relative availability, accessibility and affordability of the drug in the market. However, it is difficult to speculate further without additional research. In addition, the currently accepted practice globally requires the use of fentanyl in children, an alternative opioid to pentazocine, as a pre-anesthetic medication or post-operative analgesic [40]. This is because fentanyl had been found to relief pain better, and the analgesic effect lasted longer, than those of tramadol, pentazocine or ketorolac [41]. In addition, the US-Food and Drug Administration has given a limited approval for fentanyl use in children ≥ 2 years as an analgesic and a pre-anesthetic medication [42]. Additionally, larger studies have indicated that off-label use of fentanyl is associated with minimal AEs in children, and fentanyl is potentially safe in all pediatric age groups [43, 44].

In our study, pentazocine was administered to neonates (13.2%) for post-operative pain management or as a pre-anesthetic medication. Osifo *et al*. reported that of the 1303 pediatric patients administered pentazocine during or after surgery in Benin City, 3.8% were neonates [8]. The availability of modern and adequate ventilators at our center required for managing pentazocine-induced respiratory depression, a major cause of life-threatening morbidity or mortality in neonates, may have contributed to the increased use of pentazocine among neonates in our cohort. However, none of our patients experienced a severe or life-threatening respiratory depression that may require intubation and assisted ventilation. Nonetheless, caution should be exercised when administering pentazocine to neonates for anesthetic induction and when dose increases or repeated dosing is required. Considering the high rates of life-threatening respiratory problems associated with opioids analgesics in neonates, which is of global concern [8, 45], it is important to intensely monitor for respiratory depression among neonates using pentazocine.

Rapid breathing, followed by sleepiness/sedation/drowsiness, and fast pulse were the most common AEs to pentazocine reported in our cohort (Table 1). The fast respiratory and pulse rates reported in our cohort might have resulted from poorly managed pain due to inadequate dosing of pentazocine to patients or a normal physiological response to pain [46]. The non-use of validated pain and sedation assessment tools in our cohort might have further worsened the pain management. However, it is difficult to comment further without additional research. Although rapid breathing was uncommon in previous studies evaluating AEs of pentazocine in children, slow breathing (respiratory depression) which was observed in 24.5% of our cohort is a major finding among neonates exposed to pentazocine in Nigeria [8], and older children exposed to pentazocine in the United States [47]. Higher proportion of patients with pentazocine-induced sedation (56.6%) and vomiting (42.8%) were observed in our cohort than previously reported (27.5% and17.2%, respectively) among older children of unspecified ages in Nigeria [8]. Although both studies were retrospective, we evaluated a small cohort of 159 patients over a period of 3 years, while the comparative study evaluated a larger cohort of 1510 children over a period of 10 years. Metronidazole is a concomitant drug used by all our patients and is well known to induce nausea and vomiting in children [48, 49]. Consequently, we may have over-estimated the incidence of vomiting associated with pentazocine among our cohort. However, the comparative study [8] neither evaluated nor acknowledged the impact of such concomitant medication on the reported AEs in their study.

Nearly all the patients experienced multiple AEs with four AEs being the commonest. Most of these AEs (e.g. fast or slow pulse, fast or slow breathing, vomiting, constipation, sedation, and irritability) are common, while some (e.g. fever, cough, and generalized itching) are rare [10, 16]. Consistent with other studies, common and rare AEs have been reported with pentazocine among children undergoing tonsillectomy or abdominal surgery; vomiting, over-sedation and apprehension were among the most common AEs [8, 18, 19, 21]. However, none of the AEs experienced by our cohort of patients was severe or life threatening and did not require treatment discontinuation, medical intervention, or prolonged their hospilization. Our data, therefore, suggest that off-label use of pentazocine may be potentially safe in children after all, but they must be carefully monitored using modern ventilators where pertinent.
There is a lack of studies identifying risk factors for pentazocine-induced AEs in children. However, neonatal age and higher medication dose have been reported as major risk factors for adverse respiratory depression rescued with naloxone [50]. In spite of slow breathing, which can result in respiratory depression, being one of the most reported AEs among our cohort, demographic variables and dosing regimen of pentazocine did not significantly impact the risk of developing AEs. These findings will be strengthened by validation in a dataset from an ongoing prospective study involving a larger cohort.

We acknowledge several limitations in this study. It involves a single center and our findings may not be generalized to the entire pediatric population in Nigeria. However, we believe our findings are robust based on the relatively large sample size that we analyzed. Another limitation is the retrospective nature of the study, which, like previous AEs studies, is characterized by missing and inaccurate data [51, 52]. Similar to previous retrospective studies, we may not have complete ascertainment of all the AEs experienced by our cohort during the study period [53]. The indications for pentazocine exposure and the dosing regimen of the drug were not documented for three children, while the case files for two children were irretrievable. Consequently, the incidence of AEs may well have been under-estimated. There may be errors in the documented dosing regimen, which may bias the identified risks for AEs. Causality assessment between the AEs and pentazocine would have been useful in excluding concomitant medications as the likely cause. However, this was unnecessary in AEs studies since the untoward events may or may not be completely related to the suspected drug [54]. The use of pentazocine for a short period of 72 hours necessitated us to capture only AEs documented within a week from the first exposure. Consequently, we may have missed those AEs that presented later. Fever, tachypnea, tachycardia, nausea and vomiting that constitute a substantial number of AEs reported in this study are either physiological responses to pain or mild post-operative complications of pain, surgery, or anesthesia [46, 55, 56]. Therefore, these AEs suspected to be pentazocine-induced might have been over-estimated. Data were extracted from paper files due to lack of Electronic Medical Record system in our hospital. The tendencies for lost documents, illegible handwritings, poor text-mining, and irretrievable case files may have potentially introduced bias to the study. Upgrading to Electronic Medical Record system would likely improve data quality, more AEs detection through improved text-mining technique, and enable us to

capture data for all patients in the future studies [57]. Despite these limitations, we believe our findings are robust providing direction for the future.

5. Conclusion

Off-label use of pentazocine is common among our cohort of patients in Nigeria and was associated with multiple AEs. Most pediatric patients experienced four AEs, with increased respiratory rates being the most common. The type of surgery, gender, age at commencement of pentazocine, weight at commencement of pentazocine, total daily dose of pentazocine administered, frequency and duration of use of pentazocine were not significantly associated with the risk of experiencing slow respiratory AEs to pentazocine.

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Tables

Table1: The 631 adverse events reported among 159 children that used pentazocine postoperatively

Specific adverse events experienced per patient	**Number of adverse events experienced per patient**	**Number of patients experiencing adverse events**	**Total adverse events experienced by all patients *n*(%)**
Fast breathing, fast pulse, fever, cold and clammy skin, sedation, vomiting, and flushed skin	7	3	21 (3.3)
Fast breathing, fast pulse, fever, cold and clammy skin, sedation, constipation, and irritability	7	3	21 (3.3)
Fast breathing, fast pulse, cough, cold and clammy skin, sedation, and irritability	6	4	24 (3.8)
Slow breathing, slow pulse, cough, sedation, vomiting, and flushed skin	6	2	12 (1.9)
Fast breathing, cold and clammy skin, cough, sedation, and vomiting	5	5	25 (4.0)
Fast breathing, fast pulse, constipation, fever, and sedation	5	4	20 (3.2)
Fast breathing, constipation, sedation, vomiting, and flushed skin	5	4	20 (3.2)
Fast breathing, fast pulse, cold and clammy skin, vomiting, and sedation	5	3	15 (2.4)
Fast breathing, fast pulse, constipation, vomiting, and irritability	5	3	15 (2.4)
Fast breathing, fast pulse, constipation, sedation, and flushed skin	5	3	15 (2.4)
Fast breathing, fast pulse, generalized itching, vomiting, and irritability	5	2	10 (1.6)
Fast breathing, fast pulse, constipation, vomiting, and sedation	5	2	10 (1.6)
Fast breathing, fast pulse, cough, fever, and flushed skin	5	1	5 (0.8)
Slow breathing, slow pulse, cough, sedation, vomiting, and flushed skin	5	3	15 (2.4)
Slow breathing, slow pulse, cough, constipation, and irritability	5	3	15 (2.4)

Slow breathing, slow pulse, cold and clammy extremity, sedation, and vomiting	5	3	15 (2.4)
Fast breathing, fast pulse, constipation, and vomiting	4	6	24 (3.8)
Fast breathing, fast pulse, constipation, and irritability	4	5	20 (3.2)
Fast breathing, sedation, vomiting, and flushed skin	4	4	16 (2.5)
Fast breathing, fast pulse, sedation, and irritability	4	4	16 (2.5)
Fast breathing, cold and clammy extremity, vomiting, and irritability	4	4	16 (2.5)
Fast breathing, fast pulse, cough, and vomiting	4	3	12 (1.9)
Fast breathing, constipation, generalized itching, and irritability	4	3	12 (1.9)
Fast breathing, constipation, vomiting, and irritability	4	3	12 (1.9)
Fast breathing, fast pulse, constipation, and sedation	4	2	8 (1.3)
Fast breathing, fast pulse, cold and clammy skin, and irritability	4	2	8 (1.3)
Fast breathing, fast pulse, cough, and sedation	4	3	12 (1.9)
Slow breathing, slow pulse, sedation, and irritability	4	7	28 (4.4)
Slow breathing, slow pulse, fever, and vomiting	4	5	20 (3.2)
Slow breathing, slow pulse, vomiting, and irritability	4	2	8 (1.3)
Slow breathing, slow pulse, cough, and sedation	4	1	4 (0.6)
Slow breathing, slow pulse, constipation, and vomiting	4	1	4 (0.6)
Fast breathing, fast pulse, and sedation	3	13	39 (6.2)
Slow breathing, slow pulse, and sedation	3	7	21 (3.3)
Fast breathing, cold and clammy skin, and sedation	3	5	15 (2.4)
Fast breathing, fever, and vomiting	3	3	9 (1.4)
Fast breathing, fast pulse, and flushed skin	3	3	9 (1.4)
Fast breathing, sedation, and vomiting	3	2	6 (0.9)
Fast breathing, fast pulse, and vomiting	3	2	6 (0.9)
Slow breathing, slow pulse, and irritability	3	3	9 (1.4)
Slow breathing, slow pulse, and vomiting	3	3	9 (1.4)

Fast breathing and fast pulse	2	8	16 (2.5)
Fast pulse and sedation	2	3	6 (0.9)
Fast breathing and irritability	2	1	2 (0.3)
Slow breathing and slow pulse	2	3	6 (0.9)
Total		**159**	**631 (100.0)**

N.B. The 631 adverse events comprise rapid breathing (116), sleepiness/sedation/drowsiness (90), fast pulse (79), vomiting (68), irritability (49), slow breathing (43), weak pulse (43), constipation (42), cold and clammy skin (32), cough (25), flushed skin (23), fever (19), and generalized itching (5)

Table 2: Demographic and clinical risk factors for slow respiratory adverse event to pentazocine

Potential Risk Factor	**Adjusted Odds Ratio (95% Confidence Interval) for Slow Respiratory Rate**
Type of surgery	
Major	0.00 (0.00-0.00)
Gender	
Male	0.67 (0.08-5.74)
Weight	1.07 (0.83-1.38)
Age	1.04 (0.68-1.60)
Pentazocine dosing regimen	
Total daily dose of pentazocine (mg)	1.05 (0.99-1.11)
Frequency of dosing of pentazocine	0.00 (0.00- 0.00)
Duration of dosing	
• ≤24 hours	7.92 (0.07-847.79)
• 48 hours	8.17 (0.04- 1569.85)

Note: The model was generated using binary logistic regression, adjusted odds ratio (OR) refers to the odds ratio after each variable was included in the regression model.

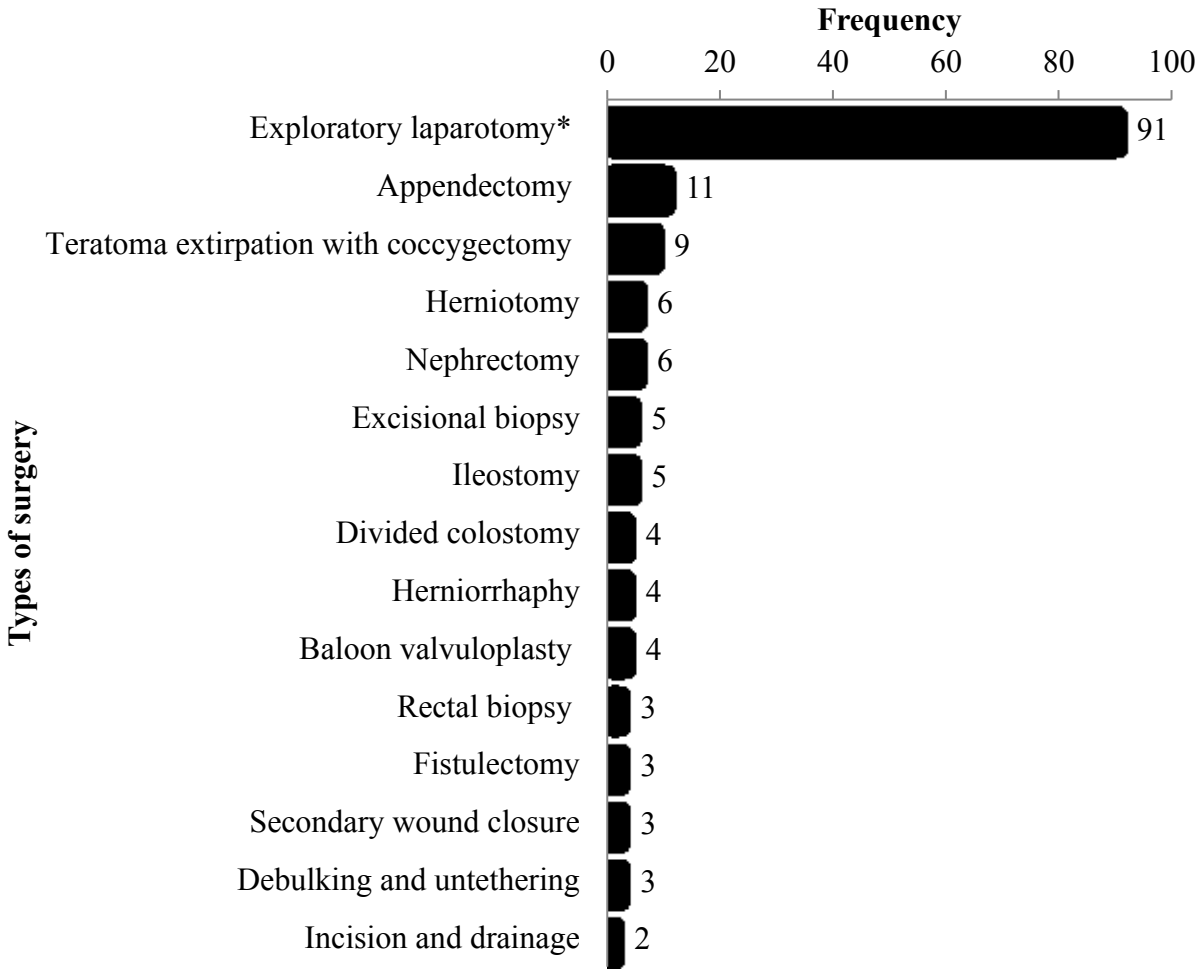

Figure 1: Types of surgery necessitating the use of pentazocine

Note: * represents exploratory laparotomy with some specific procedures including wedge resection of the bowel and repair (28), manual reduction of intussusceptions only (26), bowel resection and anastomosis (15), excisional biopsy (7), hemicolectomy (6), appendectomy (4), bowel resection and loop colostomy (3), and manual reduction of intussusceptions with appendectomy (2).