Clinical Investigation

Impact of a Drug Shortage on Medication Errors and Clinical Outcomes in the Pediatric Intensive Care Unit

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OBJECTIVES: The purpose of this study was to assess the rate of prescribing errors, resulting adverse events, and patient outcomes associated with sedation and analgesia in the pediatric intensive care unit (PICU) before and during a national shortage of fentanyl and injectable benzodiazepines.

METHODS: A retrospective chart review was performed of patients admitted to the PICU with at least 1 prescribed order for a sedative or analgesic agent during the time periods of January to February of 2011 and 2012. Initial orders for sedative and analgesic agents were identified and investigated for appropriateness of dose and were assessed for error-associated adverse events. Orders were stratified by timing in regard to clinical pharmacist on-site availability. Demographic and outcome information, including unintended extubations, ventilator days, and PICU length of stay, were gathered.

RESULTS: One hundred sixty-nine orders representing 72 patients and 179 orders representing 75 patients in 2011 and 2012, respectively, were included in analysis. No differences were found in the rate of prescribing errors in 2011 and 2012 (33 errors in 169 orders vs. 39 errors in 179 orders, respectively, p=0.603). No differences were found in rates of prescribing errors in regard to clinical pharmacist on-site availability. A significant increase was seen in unintended extubations per 100 ventilator days, with 0.15 in 2011 vs. 1.13 in 2012, respectively (p<0.001). A significant decrease was seen in ventilator days per patient (p<0.001) and PICU length of stay per patient (p=0.019).

CONCLUSIONS: There were no differences in rates of prescribing errors before versus during the fentanyl and benzodiazepine shortage.

INDEX TERMS: benzodiazepines, drug substitution, medication errors, opioid analgesic, pediatric intensive care units

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INTRODUCTION

Medication errors harm 1% to 2% of patients, with most errors originating during the prescribing process.[1] The most common prescribing error is prescribing the wrong dose, which may be associated with significant adverse events.[2] The potential for medication errors increases during drug shortages due to increased prescribing of unfamiliar agents.[3] The use of an alternative drug, dosage form, or dosage strength accounted for up to 27% of reported harmful outcomes related to drug shortages in hospitalized patients.[4]

American Society of Health System Pharmacists reported a shortage of fentanyl and the injectable benzodiazepines midazolam, lorazepam, and diazepam beginning in 2011. Reports of resolution of the shortages were unclear, due in part to discontinued production of particular preparations, increased demand, and manufacturing issues.[5,6] Opioids are often prescribed for analgesia in the pediatric intensive care unit (PICU).[7,8] Fentanyl is often chosen over other opioid agents because of its cardiovascular stability, positive effects on pulmonary vascular resistance, and ability to reduce the sympathetic stress response.[7-9] Benzodiazepines are among the most common sedatives initiated first in the PICU.[10,11] They enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid and have sedative and amnesiac properties but offer no intrinsic analgesia.[7,8]

The national shortage of fentanyl and injectable benzodiazepines was most prevalent at the study institution in January and February of 2012. With an uncertain supply of these commonly prescribed agents, allocation was prioritized to specific patient populations, and limitations were placed on the use of these agents in the PICU. Clinical pharmacists and critical care physician leadership identified potential therapeutic alternatives for initial management of pain and sedation and provided standardized algorithms to the critical care teams (Appendix Figure). This included use of other opioids, such as morphine and hydromorphone. It also necessitated use of less familiar agents for sedation including propofol, pentobarbital, ketamine, and dexmedetomidine. The purpose of this study was to evaluate the change in prescribing errors during the fentanyl and injectable benzodiazepine shortage, to assess adverse events associated with prescribing errors, and to evaluate patient outcomes related to sedation, including unintended extubations, ventilator duration, and PICU length of stay.

MATERIALS AND METHODS

A retrospective chart review was approved as exempt by review of the university's institutional review board to compare outcomes before (January to February 2011) and during (January to February 2012) the drug shortage. Initial orders for a sedative or analgesic agent were identified through the pharmacy order entry system. During the study period, the institution did not use computerized provider order entry; orders were written by prescribers in a paper chart, scanned to the pharmacy, and then entered by the pharmacist into the electronic medical record. Patients were included if they were admitted to the PICU and had an active order for a sedative or analgesic agent. Only the initial order for each agent was assessed for accuracy. Patients were excluded if they were admitted to the cardiovascular surgery or cardiac intensive care services, as the shortage agents were preferentially reserved for this population. Patients who were not mechanically ventilated were also excluded. For secondary clinical outcomes, patients were excluded if they were chronically ventilator-dependent.

The primary endpoint was the rate of prescribing errors before versus during the drug shortage. Secondary medication error outcomes included error-associated differences in adverse events before and during the drug shortage and the rate of medication errors during clinical pharmacist on-site availability (Monday through Friday from 8 am to 5 pm) compared to off-site availability (all other times). At the study institution, clinical pharmacists were available to their subspecialty service by pager at all hours of the day, even if the pharmacist was not available on-site. Clinical pharmacists did not keep a log of calls received during off-site hours. Secondary clinical outcomes investigated included unintended extubations, ventilator days, and PICU length of stay, defined as the calendar days from PICU admission to transfer to floor, discharge home, or death.

Prescribing errors included any orders outside the predefined appropriate dosing for each medication (Table 1). Opioid conversions were assessed with any prior opioid use.[12,13] Prescribing errors were classified as underdosing, prescribing a dose lower than an appropriate weight-based dose, or overdosing, prescribing a dose greater than an appropriate weight-based or absolute maximum dose. After a prescribing error was identified, the patient's chart was assessed for predefined adverse events specific to the medication in error (Table 2). Hypotension, hypertension, bradycardia, and tachycardia were defined using the Pediatric Algorithm for Life Support guidelines and recorded if the event occurred within fifteen minutes after an intravenous administration or 2 hours after an enteral administration.[14] Metabolic acidosis was defined as a pH less than 7.35 with a bicarbonate concentration below 22 mmol/L and a partial pressure of carbon dioxide (pCO_2) between 35 and 45 mm Hg that occurred 24 hours after an initial dose through medication discontinuation. Naloxone and flumazenil administration were recorded if the patient received the medication during any time of their original prescribed therapy. Any additional actions required, including dose increase or decrease or the need for an additional sedative or analgesic medication, were also recorded.

The chi-squared test was used to analyze sex, the rate of prescribing errors, error-associated adverse events, and clinical pharmacist on-site availability. The Mann-Whitney *U* test was used to compare age, weight, ventilator days, and PICU length of stay. Hospital mortality, defined as death at any point during the same hospital

Table 1. Appropriate Ranges for Initial Medication Doses*

	Bolus, Weight-Based	Bolus, Maximum	Continuous Infusion, Weight-Based	Continuous Infusion, Maximum
Fentanyl	1-2 mcg/kg	50 mcg	1-2 mcg/kg/hr	100 mcg/hr
Morphine	0.05-0.2 mg/kg	5 mg	0.01-0.04 mg/kg/hr	1.5 mg/hr
Hydromorphone	0.01-0.015 mg/kg	0.6 mg	0.003-0.005 mg/kg/hr	0.2 mg/hr
Midazolam	0.05-0.1 mg/kg	5 mg†	0.06-0.12 mg/kg/hr	7 mg/hr‡
Lorazepam IV	0.025-0.1 mg/kg	4 2 mg†	0.025-0.1 mg/kg/hr†	2 mg/hr†
Lorazepam PO	0.02-0.1 mg/kg	2 mg	–	–
Dexmedetomidine	–	–	0.2-1 mcg/kg/hr	–
Ketamine	0.5-2 mg/kg	100 mg	5-20 mcg/kg/min	–
Pentobarbital	1-2 mg/kg	100 mg	0.5-6 mg/kg/hr	–
Propofol	0.5-1 mg/kg	50 mg	5-50 mcg/kg/min†	–

*Pediatric Lexi-Drugs,[20] unless specifically noted
†Lexi-Drugs[20]
‡Package insert[21]

admission, and unintended extubations were compared using the Fisher exact test. The a priori level of significance was <0.05.

RESULTS

Seven hundred fifty orders representing 208 patients were identified from January to February 2011. Five hundred eighty-one orders were excluded, whereas 169 orders were included, representing 72 patients (Figure). In 2012, 785 orders representing 226 patients were identified. Six hundred six orders were excluded, resulting in 179 orders representing 75 patients being included (Figure). Patient characteristics were similar between the groups, except for hospital mortality, which was statistically higher in the 2011 group (Table 3).

Fentanyl was the analgesic agent most commonly prescribed in 2011, representing 25% of total orders. During the shortage, fentanyl use decreased by 10%, and prescriptions of other opioids increased, including morphine and hydromorphone (Table 4). The benzodiazepines

Table 2. Reviewed Adverse Events by Medication

	Hypotension	Hypertension	Bradycardia	Tachycardia	Naloxone	Flumazenil	Metabolic Acidosis	Rhabdomyolysis	Cardiac Failure	Acute Kidney Injury	Hyperosmolarity
Fentanyl			x		x						
Morphine	x				x						
Hydromorphone	x				x						
Midazolam	x					x					
Lorazepam						x	x			x	x
Dexmedetomidine	x		x								
Ketamine	x	x		x							
Pentobarbital	x		x				x			x	x
Propofol	x		x				x	x	x		

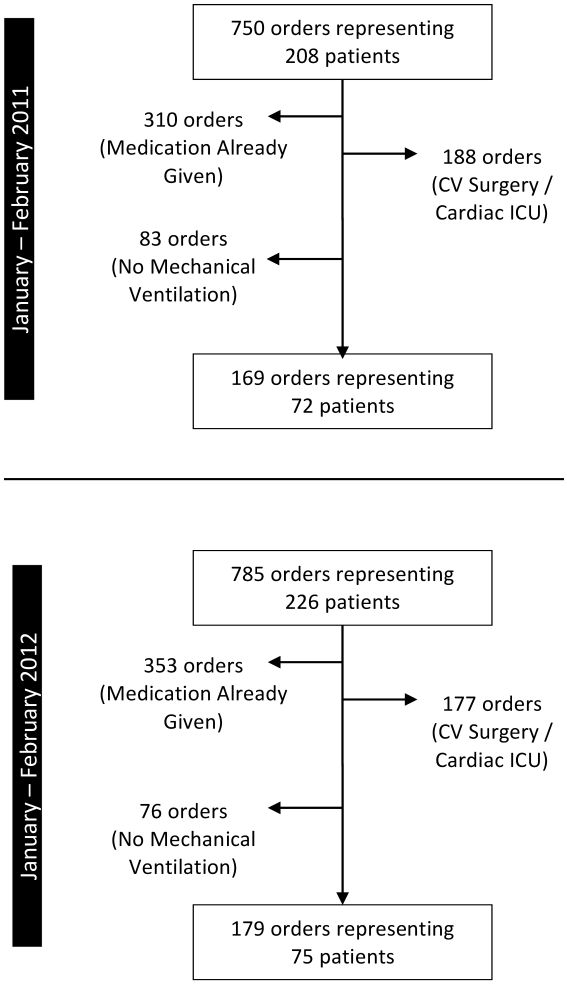

Figure. Patient enrollment.
CV, cardiovascular; ICU, intensive care unit.

midazolam and lorazepam equaled 38% of orders in 2011 versus 29% in 2012.

No differences were found between the rate of prescribing errors for initial orders in 2011 and that in 2012 (p=0.603) (Table 5). Fifty-eight-percent of all errors were due to underdosing, whereas 42% of errors were due to overdosing (Table 6). Morphine, midazolam, and enteral lorazepam were more commonly underdosed than overdosed.

A total of 23% of patients experienced an error-associated adverse event in 2011 and 34% in 2012 (p=0.333) (Table 7). Hypotension was the most common adverse event followed by hypertension. One case of bradycardia occurred with pentobarbital administration, and 1 patient who received a ketamine bolus became tachycardic. One patient who was receiving lorazepam experienced metabolic acidosis. A patient receiving continuous infusion (CI) of fentanyl, 3 mcg/kg/hr, required naloxone administration when he became unresponsive. Flumazenil was administered to that same patient, who was also receiving CI midazolam, 0.1 mg/kg/hr. This dose was within the predefined appropriate CI rate, but the patient also received multiple midazolam boluses.

There were no differences between 2011 and 2012 in orders requiring additional actions, with 60% and 55% of orders requiring an adjustment, respectively (Table 5). When orders were stratified based upon clinical pharmacist on-site versus off-site availability, no differences in rates of prescribing errors were noted (21 errors in 143 orders vs. 51 errors in 222 orders, respectively, p=0.152). For the secondary clinical outcomes, patients who were chronically ventilator-dependent were excluded (n=9 in 2011, n=10 in 2012). There was a significant increase in unintended extubations per 100 ventilator days, with 0.15 extubations in 2011 vs. 1.13 extubations in 2012 (p<0.001). Significant decreases were seen in ventilator days per patient, with 6 days in 2011 vs. 2.5 days in 2012 (p<0.001) and PICU length of stay per patient from 7.5 days to 6.0 days (p=0.019) in 2011 to 2012, respectively.

DISCUSSION

The drug shortage crisis has affected all healthcare organizations, with an ever-growing number of critically important medications in short supply. When assessing a drug shortage, position statements from several organizations recommend identifying therapeutic alternatives early, placing limitations on use by prioritizing patients, establishing ongoing communication with staff, and proactively monitoring adverse outcomes.[3,15,16] In the PICU, the recent shortage of fentanyl and injectable benzodiazepines required many substitutions for these commonly prescribed agents.

At the study institution, the clinical pharmacists identified potential therapeutic alternatives for initial management of sedation and, in conjunction with the critical care physician leadership, developed a standardized approach to conservation of shortage medications. The clinical pharmacists prepared printed references containing algorithms for use, dosing recom-

Table 3. Patient Characteristics

Characteristic	2011 (n=72)	2012 (n=75)	p
Median plus IQR age (yr)*	1.0 (0.65-8.25)	1.0 (0.29-6.5)	0.892
No. of males (%)†	40 (56%)	36 (48%)	0.564
Median plus IQR weight (kg)*	11.2 (6.4-26.3)	12.0 (5.4-20.7)	0.991
Incidence of hospital mortality (%)‡	11 (15%)	3 (4%)	0.025

IQR, interquartile range
* Mann-Whitney U test
† Chi-squared test
‡ Fisher's exact test

mendations, and monitoring parameters for the alternative sedative and analgesic agents. They also provided in-person prescriber education. Both fentanyl and midazolam were preferentially prioritized to the cardiovascular surgery and cardiac intensive care unit patients. Fentanyl was reserved for hemodynamically unstable patients requiring opioid analgesia, thereby causing an overall increase in morphine and hydromorphone use during the shortage. Midazolam was reserved for specific populations as well, including patients requiring neuromuscular blockade who could not receive another appropriate agent (see Appendix).

Overall rates of prescribing errors were similar to the rates found in a tertiary children's hospital PICU, reported as 21% in a 2012 study by Maat et al.[17] However, our rates reflected only the initial orders for each medication and do not account for dose titrations after initial prescribing. Only initial orders were assessed in order to limit variability secondary to clinical titrations due to patient response or adverse events. We hypothesized an increase in prescribing errors of these initial orders during the shortage, though no difference was seen. Ongoing communication by the clinical pharmacist with provision of detailed medical references as well as routine face-to-face education to prescribers both during patient care rounds and throughout the day might have decreased errors and contributed to the similarity in the rates of prescribing errors in 2011 and 2012. Availability of the clinical pharmacist by pager at all hours of the day might have further mitigated this difference. Although clinical pharmacists were available by pager at all times during both time periods, no formal call log was maintained; therefore, it was not possible to objectively assess whether the number sedation-related calls increased during this time.

The significant differences in mortality between the groups might have affected the data relating to clinical outcomes. Additional investigation of deceased patients found that, in 2011, several

Table 4. Medication Orders Before and During Shortage

	No. of Orders in 2011, n=169	No. of Orders in 2012, n=179	p
Fentanyl	42 (25%)	26 (15%)	0.015
Morphine	16 (9%)	38 (21%)	0.002
Hydromorphone	2 (1%)	9 (5%)	0.040
Midazolam	40 (24%)	10 (6%)	0.010
Lorazepam IV	24 (14%)	26 (15%)	0.920
Lorazepam PO	0 (0%)	15 (8%)	0.001
Dexmedetomidine	38 (22%)	48 (27%)	0.348
Ketamine	4 (2%)	3 (2%)	0.717
Pentobarbital	1 (1%)	4 (2%)	0.372
Propofol	2 (1%)	1 (1%)	0.613

IV, intravenous; PO, administered orally

Table 5. Prescribing Errors for Initial Orders by Medication

Outcome	No. of Errors/ Total no. of Rx, 2011	No. of Errors/ Total no. of Rx, 2012	p
Total prescribing errors*	33/169 (20%)	39/179 (22%)	0.603
Fentanyl	8/42 (19%)	6/26 (23%)	0.689
Morphine	7/16 (44%)	9/38 (24%)	0.194
Hydromorphone	0/2 (0%)	4/9 (44%)	0.491
Midazolam	9/40 (23%)	4/10 (40%)	0.420
Lorazepam IV	2/24 (8%)	6/26 (23%)	0.250
Lorazepam PO	–	5/15 (33%)	–
Dexmedetomidine	4/38 (11%)	2/48 (4%)	0.399
Ketamine	1/4 (25%)	1/3 (33%)	0.714
Pentobarbital	1/1 (100%)	2/4 (50%)	0.600
Propofol	1/2 (50%)	0/1 (0%)	0.667

* Total prescribing errors

patients were admitted with severe underlying chronic diseases such as spinal muscular atrophy, metabolic origin dilated cardiomyopathy, and severe aplastic anemia. These likely contributed to increased hospital mortality, a longer ventilator duration, and increased PICU length of stay seen in 2011. Due to the retrospective nature of the study, severity of illness scores could not be calculated for all patients. However, differences in hospital mortality indicate there might have been differences in the severity of illnesses between the 2 study periods, which also could have influenced the differences in PICU length of stay and ventilator days.

There were several other limitations to this study. First, the retrospective nature of the study limited the ability to identify adverse events due to variability in charting. Furthermore, causality of each adverse event could not be assigned to a specific agent. We could not account for all additional factors that could have affected duration of mechanical ventilation, including delirium or use of neuromuscular blocking agents. However, dexmedetomidine has been associated with decreased ventilator days compared with midazolam in the adult ICU.[18,19] Increased prescribing of dexmedetomidine during the benzodiazepine shortage, although not statistically significant, might have contributed to the decreased duration of mechanical ventilation in 2012. Additionally, bed availability can limit transfer out of the PICU, which might have influenced length of stay. Although the number and training level of prescribers remained consistent in the PICU, prescribers in the 2 periods were not identical. Standard hours were used to estimate clinical pharmacist on-site availability, but it was not possible to truly assess the clinical pharmacists' on-site presence. Furthermore, we were unable to determine interventions at the time each order was written from either the clinical or staff pharmacist.

There was a significant increase in unintended extubations per 100 ventilator days. This may indicate that, although appropriate therapy was initiated at similar rates before and after the shortage, when unfamiliar medications were used, prescribers were less able to titrate therapy to appropriate sedation, resulting in undersedation and increased chance for unintended extubations. During the study period, validated sedation scores were not optimally and reliably recorded and could not be retrospectively evaluated to determine the appropriateness of sedative titration or the differences in achieving sedation goals before and during the shortage period.

CONCLUSIONS

In conclusion, we found no increase in prescribing errors for initial sedative and analgesic orders during the fentanyl and benzodiazepine shortage. These outcomes suggest that early awareness of drug shortage, identification of potential therapeutic alternatives, and appropri-

Table 6. Prescribing Errors by Type

Medication	2011 No. of Errors/ Total no. of Rx, (%)	2012 No. of Errors/ Total no. of Rx,(%)	Total No. of Errors/ Total no. of Rx (%)
Total*			
Underdosed	19/33 (58%)	23/39 (59%)	42/72 (58%)
Overdosed	14/33 (42%)	16/39 (41%)	30/72 (42%)
Fentanyl			
Underdosed	3/8 (37%)	3/6 (50%)	6/14 (43%)
Overdosed	5/8 (63%)	3/6 (50%)	8/14 (57%)
Morphine			
Underdosed	6/7 (86%)	7/9 (78%)	13/16 (81%)
Overdosed	1/7 (14%)	2/9 (22%)	3/16 (19%)
Hydromorphone			
Underdosed	–	2/4 (50%)	2/4 (50%)
Overdosed	–	2/4 (50%)	2/4 (50%)
Midazolam			
Underdosed	6/9 (67%)	4/4 (100%)	10/13 (77%)
Overdosed	3/9 (33%)	0/4 (0%)	3/23 (23%)
Lorazepam IV			
Underdosed	1/2 (50%)	1/6 (17%)	2/8 (25%)
Overdosed	1/2 (50%)	5/6 (83%)	6/8 (75%)
Lorazepam PO			
Underdosed	–	5/5 (100%)	5/5 (100%)
Overdosed	–	0/5 (0%)	0/5 (0%)
Dexmedetomidine			
Underdosed	2/4 (50%)	1/2 (50%)	3/6 (50%)
Overdosed	2/4 (50%)	1/2 (50%)	3/6 (50%)
Ketamine			
Underdosed	0/1 (0%)	0/1 (0%)	0/2 (0%)
Overdosed	1/1 (1%)	1/1 (1%)	2/2 (100%)
Pentobarbital			
Underdosed	1/1 (100%)	0/2 (0%)	1/3 (33%)
Overdosed	0/1 (0%)	2/2 (100%)	2/3 (67%)
Propofol			
Underdosed	0/1 (0%)	–	0/1 (0%)
Overdosed	1/1 (100%)	–	1/1 (100%)

* Total number of prescribing underdosed errors versus the number of prescribing overdosed errors (p=0.046).

ate communication and education may mitigate the potential for increased prescribing errors that may be seen during drug shortages. Future study and quality improvement work should focus on prospectively evaluating steps that can be implemented to mitigate the risk of prescribing errors, including mechanisms that can be implemented with computerized order entry systems to help guide prescribers in the use of unfamiliar medications.

Table 7. Error-Associated Adverse Events and Dose Adjustments

Outcome	2011 No. of Events and Adjustments (n=52)	2012 No. of Events and Adjustments (n=44)
Total adverse events*	12 (23%)	15 (34%)
Hypotension	9 (26%)	10 (23%)
Hypertension	0 (0%)	2 (5%)
Bradycardia	0 (0%)	1 (2%)
Tachycardia	1 (2%)	0 (0%)
Metabolic acidosis	0 (0%)	1 (2%)
Naloxone administration	1 (2%)	0 (0%)
Flumazenil administration	1 (2%)	0 (0%)
Total additional actions*	31 (60%)	24 (55%)
Dose increase	11 (21%)	9 (20%)
Dose decrease	0 (0%)	1 (2%)
Additional medication	20 (38%)	14 (32%)

* Total adverse events and additional actions in 2011 versus those in 2012 (p=not significant).

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Abbreviations CV, cardiovascular; CI, continuous infusion; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; pCO_2, partial pressure of carbon dioxide; PICU, pediatric intensive care unit; PO, administered orally

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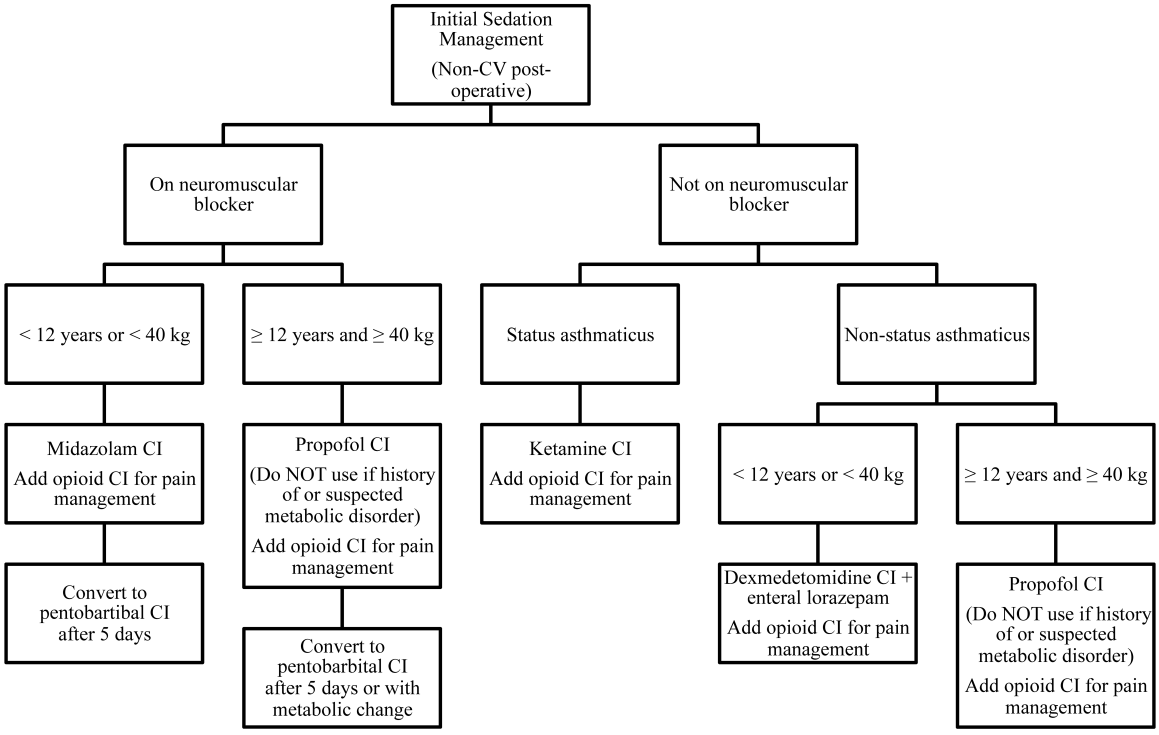

Appendix. Initial sedation management algorithm during drug shortage.
CV, cardiovascular; CI, continuous infusion.