

**Article title:** Drug-drug interactions involving high-alert medications that lead to interaction-associated symptoms in pediatric intensive care patients: a retrospective study

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Online Resource 1: Definition of symptoms detected after potential drug-drug interactions involving high-alert medication

Symptom	Definition of symptom
Decreased blood pressure	<p>Blood pressure falls below the lower age-dependent standard range for diastolic or diastolic blood pressure<sup>a</sup></p> <ul style="list-style-type: none"> <li>• &lt; 12 months: &lt; 37/72 mmHg (diastolic/systolic)</li> <li>• 1 – &lt; 4 years: &lt; 46/80 mmHg (diastolic/systolic)</li> <li>• 4 - &lt; 7 years: &lt; 47/80 mmHg (diastolic/systolic)</li> <li>• 7 - &lt; 11 years: &lt; 52/83 mmHg (diastolic/systolic)</li> <li>• 11 - &lt; 13 years: &lt; 58/95 mmHg (diastolic/systolic)</li> <li>• ≥14 years: &lt; 55/100 mmHg (diastolic/systolic)</li> </ul>
Decreased heart rate	<p>Heart rate falls below the lower age-dependent standard range for heart rate<sup>a</sup></p> <ul style="list-style-type: none"> <li>• &lt; 2 years: &lt; 80 bpm</li> <li>• 2 – &lt; 10 years: &lt; 60 bpm</li> <li>• ≥10 years: &lt; 50 bpm</li> </ul>
Fever	<p>Body temperature exceeds the upper age-dependent standard range for fever:</p> <ul style="list-style-type: none"> <li>• &lt; 3 months: &gt; 38.0 °C</li> <li>• ≥ 3 months: &gt; 38.5 °C</li> </ul>
Hypercalcemia	<p>Blood calcium exceeds the upper age-dependent reference range</p> <ul style="list-style-type: none"> <li>• &lt; 1 month: &gt; 2.78 mmol/l</li> <li>• ≥ 1 month: &gt; 2.6 mmol/l</li> </ul>
Hyperkalemia	<p>Blood potassium exceeds the upper age-dependent reference range</p> <ul style="list-style-type: none"> <li>• &lt; 1 months: &gt; 6.1 mmol/l</li> <li>• 1 - 12 months: years: &gt; 5.8 mmol/l</li> <li>• ≥ 1 year: &gt; 5.2 mmol/l</li> </ul>
Hypocalcemia	<p>Blood calcium falls below the lower reference range</p> <ul style="list-style-type: none"> <li>• &lt; 1 month: &lt; 1.76 mmol/l</li> <li>• ≥ 1 month: &lt; 2.1 mmol/l</li> </ul>
Hypokalemia	<p>Blood potassium falls below the lower age-dependent reference range</p> <ul style="list-style-type: none"> <li>• &lt; 1 month: &lt; 3.6 mmol/l</li> <li>• 1 - 12 months: years: &lt; 3.7 mmol/l</li> <li>• ≥ 1 year: &lt; 3.1 mmol/l</li> </ul>

Symptom	Definition of symptom
Hypomagnesemia	<p>Blood magnesium falls below the lower age-dependent reference range</p> <ul style="list-style-type: none"> <li>• 0 - 6 days: &lt; 0.48 mmol/l</li> <li>• ≥ 6 days: &lt; 0.65 mmol/l</li> </ul>
Hyponatremia	<p>Blood sodium falls below the lower age-dependent reference range</p> <ul style="list-style-type: none"> <li>• &lt; 1 months: &lt; 132 mmol/l</li> <li>• 2 – 6 months: &lt; 129 mmol/l</li> <li>• &gt; 6 months: &lt; 132 mmol/l</li> </ul>
Increased blood pressure	<p>Blood pressure exceeds the upper age-dependent standard range for diastolic or diastolic blood pressure<sup>a</sup></p> <ul style="list-style-type: none"> <li>• &lt; 12 months: &gt; 56/104 mmHg (diastolic/systolic)</li> <li>• 1 – &lt; 4 years: &gt; 79/113 mmHg (diastolic/systolic)</li> <li>• 4 - &lt;7 years: &gt; 79/115 mmHg (diastolic/systolic)</li> <li>• 7 - &lt; 11 years: &gt; 83/122 mmHg (diastolic/systolic)</li> <li>• 11 - &lt; 13 years: &gt; 88/136 mmHg (diastolic/systolic)</li> <li>• ≥14 years: &gt; 77/127 mmHg (diastolic/systolic)</li> </ul>
Increased heart rate	<p>Heart rate exceeds the upper age-dependent standard range for heart rate<sup>a</sup></p> <ul style="list-style-type: none"> <li>• 0 - &lt; 2 years: &gt; 180 bpm</li> <li>• 2 - &lt; 3 years: &gt; 150 bpm</li> <li>• 3 - &lt; 10 years: &gt; 140 bpm</li> <li>• 10 - &lt; 13 years: &gt; 120 bpm</li> <li>• ≥ 13 years: &gt; 110 bpm</li> </ul>
Increased PTH	Blood PTH exceeds the upper reference range > 55 pg/ml
Tachypnea	<p>Respiratory exceeds the upper age-dependent standard range for respiratory rate<sup>a</sup></p> <ul style="list-style-type: none"> <li>• &lt; 1 month: &gt; 45 breaths/min</li> <li>• 1 month - &lt; 1 year: &gt; 40 breaths/min</li> <li>• 1 - &lt; 2 years: &gt; 35 breaths/min</li> <li>• 2 - &lt; 5 years: &gt; 30 breaths/min</li> <li>• 5 - &lt; 12 years: &gt; 25 breaths/min</li> <li>• ≥ 12 years: &gt; 20 breaths/min</li> </ul>

a: Physicians had the possibility to adjust the individual range according to the patient's health condition.  
bpm: beats per minute; mmHG: millimeter of mercury, min: minute, mmol/l: millimoles per liter, pg/ml: picogram per milliliter; PTH: Parathyroid hormone

## Online Resource 2: Sedative drugs administered during the study period

Sedative drugs <sup>a</sup>	Number of patient days with sedative, n (%) ( <i>N</i> =3,788 patient days)	Number of patients with sedative, n (%) ( <i>N</i> =315 patients)
Midazolam	1,011 (26.7)	173 (54.9)
Clonidine	415 (11.0)	30 (9.5)
Phenobarbital	405 (10.7)	65 (20.6)
Levomepromazine	247 (6.5)	38 (12.1)
Ketamine	173 (4.6)	71 (22.5)
Propofol	84 (2.2)	40 (12.7)

a: Only drugs that are sedatives according to the Anatomical-Therapeutic-Chemical (ATC) classification were considered.

Online Resource 3: Frequency of potential drug-drug interactions administered on at least 2% of patient days and their classification in the drug information databases UpToDate and Drugs.com

Potential drug-drug interaction		Number of patient days with the interaction, n (%) (N=3,788 patients)	Classification	
Drug 1	Drug 2		UpToDate <sup>b</sup>	Drugs.com <sup>c</sup>
Potassium salts <sup>a</sup>	Metamizole	972 (25.7)	C	n/a
Potassium salts <sup>a</sup>	Furosemide	830 (21.9)	B	n/a
Midazolam <sup>a</sup>	Metamizole	818 (21.6)	C	n/a
Potassium salts <sup>a</sup>	Heparin	641 (16.9)	C	n/a
Midazolam <sup>a</sup>	Ranitidine	571 (15.1)	n/a	Moderate
Midazolam <sup>a</sup>	Magnesium sulfate	437 (11.5)	C	n/a
Fentanyl <sup>a</sup>	Midazolam <sup>a</sup>	365 (9.6)	D	Moderate
Fentanyl <sup>a</sup>	Furosemide	318 (8.4)	C	Moderate
Fentanyl <sup>a</sup>	Metamizole	317 (8.4)	C	n/a
Potassium salts <sup>a</sup>	HCT	314 (8.3)	B	n/a
Vancomycin <sup>a</sup>	Metamizole	283 (7.5)	C	n/a
Clonidine <sup>a</sup>	Furosemide	276 (7.3)	C	n/a
Clonidine <sup>a</sup>	Magnesium sulfate	263 (6.9)	C	n/a
Fentanyl <sup>a</sup>	Magnesium sulfate	257 (6.8)	C	n/a
Epinephrine <sup>a</sup>	Albuterol	247 (6.5)	C	Moderate
Phenobarbital <sup>a</sup>	Furosemide	243 (6.4)	C	Moderate
Vancomycin <sup>a</sup>	Furosemide	233 (6.2)	n/a	Moderate
Clonidine <sup>a</sup>	Midazolam <sup>a</sup>	228 (6.0)	C	Moderate
Digoxin <sup>a</sup>	Cholecalciferol	223 (5.9)	C	Moderate
Digoxin <sup>a</sup>	Furosemide	223 (5.9)	n/a	Moderate
Midazolam <sup>a</sup>	Phenobarbital <sup>a</sup>	221 (5.8)	C	Moderate
Potassium salts <sup>a</sup>	Phenobarbital <sup>a</sup>	220 (5.8)	B	n/a
Digoxin <sup>a</sup>	HCT	206 (5.4)	n/a	Moderate
Midazolam <sup>a</sup>	Levomepromazine	195 (5.1)	D	n/a
Phenobarbital <sup>a</sup>	Magnesium sulfate	192 (5.1)	C	n/a
Midazolam <sup>a</sup>	HCT	188 (5.0)	n/a	Moderate

Potential drug-drug interaction		Number of patient days with the interaction, n (%) (N=3,788 patients)	Classification	
Drug 1	Drug 2		UpToDate <sup>b</sup>	Drugs.com <sup>c</sup>
Midazolam <sup>a</sup>	Theophylline	175 (4.6)	C	Minor
Potassium salts <sup>a</sup>	Levomepromazine	173 (4.6)	X	Major
Epinephrine <sup>a</sup>	Xylometazoline	172 (4.5)	C	n/a
Potassium salts <sup>a</sup>	Dimenhydrinate	171 (4.5)	X	Major
Digoxin <sup>a</sup>	Metamizole	169 (4.5)	C	n/a
Midazolam <sup>a</sup>	Ketamine	168 (4.4)	C	Major
Midazolam <sup>a</sup>	Levetiracetam	166 (4.4)	C	Moderate
Potassium salts <sup>a</sup>	Levetiracetam	161 (4.3)	B	n/a
Clonidine <sup>a</sup>	Phenobarbital <sup>a</sup>	159 (4.2)	C	Moderate
Digoxin <sup>a</sup>	Acetylsalicylic acid	158 (4.2)	n/a	Moderate
Phenobarbital <sup>a</sup>	Cholecalciferol	157 (4.1)	n/a	Moderate
Potassium salts <sup>a</sup>	Ipratropium	152 (4.0)	X	n/a
Fentanyl <sup>a</sup>	Phenobarbital <sup>a</sup>	139 (3.7)	D	Major
Digoxin <sup>a</sup>	Calcium gluconat	138 (3.6)	C	Major
Fentanyl <sup>a</sup>	Levomepromazine	130 (3.4)	D	Moderate
Potassium salts <sup>a</sup>	Pregabalin	130 (3.4)	B	n/a
Potassium salts <sup>a</sup>	Enoxaparin	126 (3.3)	C	n/a
Potassium salts <sup>a</sup>	Ibuprofen	113 (3.0)	C	Moderate
Digoxin <sup>a</sup>	Midazolam	111 (2.9)	n/a	Moderate
Digoxin <sup>a</sup>	Heparin	108 (2.9)	n/a	Minor
Clonidine <sup>a</sup>	Fentanyl <sup>a</sup>	107 (2.8)	D	Minor
Phenobarbital <sup>a</sup>	Levothyroxine	107 (2.8)	C	Moderate
Epinephrine <sup>a</sup>	Digoxin <sup>a</sup>	104 (2.7)	n/a	Moderate
Phenobarbital <sup>a</sup>	Levetiracetam	103 (2.7)	C	Moderate
Phenobarbital <sup>a</sup>	Theophylline	103 (2.7)	C	Moderate
Epinephrine <sup>a</sup>	Levothyroxin	101 (2.7)	n/a	Moderate
Midazolam <sup>a</sup>	Dexamethasone	101 (2.7)	B	Minor
Digoxin <sup>a</sup>	Pantoprazole	89 (2.3)	B	Moderate

Potential drug-drug interaction		Number of patient days with the interaction, n (%) (N=3,788 patients)	Classification	
Drug 1	Drug 2		UpToDate <sup>b</sup>	Drugs.com <sup>c</sup>
Midazolam <sup>a</sup>	Pregabalin	88 (2.3)	C	Moderate
Fentanyl <sup>a</sup>	Acetaminophen	87 (2.3)	B	n/a
Midazolam <sup>a</sup>	Dimenhydrinate	87 (2.3)	C	Moderate
Tacrolimus <sup>a</sup>	Metamizole	85 (2.2)	X	n/a
Fentanyl <sup>a</sup>	Sildenafil	84 (2.2)	n/a	Moderate
Phenobarbital <sup>a</sup>	Levomepromazine	83 (2.2)	X	Moderate
Vancomycin <sup>a</sup>	Cefotaxime	83 (2.2)	n/a	Moderate
Clonidine <sup>a</sup>	Propranolol	82 (2.2)	D	Major
Phenobarbital <sup>a</sup>	HCT	81 (2.1)	C	Moderate
Fentanyl <sup>a</sup>	HCT	80 (2.1)	C	Moderate
Phenobarbital <sup>a</sup>	Domperidone	79 (2.1)	C	n/a
Tacrolimus <sup>a</sup>	Mycophenolic acid	78 (2.1)	B	n/a
Tacrolimus <sup>a</sup>	Prednisolone	76 (2.0)	C	n/a

HCT: Hydrochlorothiazide; n/a: Not applicable (not listed in the respective database)

a: Categorized as high-alert medication for hospitalized pediatric patients according to Schilling et al. [6]

b: Classification used in UpToDate: “D – Consider therapy modification; C – Monitor therapy; B – No action needed. Agents may interact with each other.”

c: Classification used in Drugs.com: “Major – Avoid combinations; Moderate – Usually avoid combination. Use it only under special circumstances; Minor – Take steps to circumvent the interaction risk and/or establish a monitoring plan.”