Levomepromazine for difficult sedation in pediatric intensive care

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Abstract. Sedation and analgesia using opioids and benzodiazepines is frequently required in critically ill children to minimize pain and anxiety. In some patients, difficult sedation occurs when tolerance or unacceptable side effects limit the efficacy of conventional analgo-sedative treatment. We describe seven patients (age range 1 to 17 yr) where difficult sedation was successfully managed with enteral levomepromazine (LMZ). LMZ is a neuroleptic antipsychotic agent that exhibits potent analgo-sedative properties without respiratory depression, through non-opioid and non-benzodiazepine pathways. We describe its use in our pediatric intensive care unit to control agitation in patients with known behavioral disorders who frequently pose a significant sedation challenge. We also illustrate its successful use in cases of withdrawal syndrome and delirium, and discuss the association of fever and its distinction from neuroleptic malignant syndrome in two patients. LMZ should be considered as a useful sedative in critically ill children where difficult sedation occurs and conventional agents are exhausted.

Keywords: Methotrimeprazine, antipsychotic agents, deep sedation, psychomotor agitation, pediatric intensive care units, neuroleptic malignant syndrome, substance withdrawal syndrome, delirium

1. Introduction

Analgo-sedative drugs are frequently required in critically ill children to minimize distress, pain and anxiety, and to facilitate mechanical ventilation. Typically opioids and benzodiazepines are used but propofol, clonidine, ketamine, antihistamines and many others have been described in various combinations [1, 2]. Prolonged or high-dose sedation with these drugs commonly leads to tolerance, dependence, withdrawal, and in extreme cases cardiovascular instability and even death [3–6].

We describe the use of levomepromazine (LMZ) as a safe strategy for rapid sedation control to avoid these deleterious side effects and minimize polypharmacy. LMZ, also known as methotrimeprazine, is an antipsychotic phenothiazine with analgesic, anti-emetic, and strong sedative effects [7, 8]. We give details on its use in selected patients where difficult sedation and/or extreme agitation occurred despite exhausting conventional analgo-sedative agents.

2. Materials and methods

We identified seven patients who received LMZ for extreme agitation or difficult sedation in our mixed medical/surgical tertiary pediatric intensive care unit (PICU) between 2003 and 2011. Difficult sedation was defined as an inability to achieve adequate depth

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of sedation with conventional agents, without significant side effects and increased risk of drug tolerance or withdrawal. Our standardized sedation guideline entails first line therapy that has previously been shown to produce acceptable sedation in 82% of study hours [9]. This was achieved with intravenous (IV) morphine (20 to 40 µg/kg/hr), enteral clonidine (5 µg/kg/8 hr), regular paracetamol, and consideration for intermittent IV lorazepam boluses (0.1 mg/kg). As second line therapy enteral clonidine was replaced with an IV clonidine infusion (up to 2 µg/kg/hr) and third line agents included short term propofol infusions (maximum 4 mg/kg/hr) if these were necessary. If difficult sedation occurred LMZ was used via the enteral route using scored 25 mg tablets (Nozinan[®], Sanofi-Aventis) dissolved in water at an initial dose approximating 0.25 mg/kg (rounded to nearest scoring size). The dose was doubled every 8 hr to a maximum of 2 mg/kg per dose, if necessary. The enteral route was chosen over IV administration so as to minimize the risk of any potentially hypotensive effects.

3. Results

3.1. Difficult sedation in patients that required prolonged ventilation (Table 1)

3.1.1. Case 1

A 1-year-old child underwent a laryngotracheal reconstruction for subglottic stenosis and required ventilation immobilization for 3 days postoperatively. Agitation and restlessness prompted escalation to morphine (40 µg/kg/hr), clonidine (1.5 µg/kg/hr) and lorazepam boluses. Due to difficult sedation, LMZ was started at 0.25 mg/kg and then escalated to 0.5 mg/kg for a subsequent two doses (8 hr). This controlled sedation and agitation effectively, allowing reduction of morphine to 20 µg/kg/hr without further doses of lorazepam. LMZ was discontinued due to the development of a fever with nosocomial pneumonia, after which agitation recurred. There was no evidence for neuroleptic malignant syndrome.

3.1.2. Case 2

A child of 2 yr with chronic lung disease required mechanical ventilation due to aspiration pneumonia. Difficult sedation occurred despite morphine (40 µg/kg/hr) and clonidine (1 µg/kg/hr) infusions, and regular diazepam. Propofol was commenced on day

3 at 3.5 mg/kg/hr but sedation remained inadequate. LMZ (0.5 mg/kg) was commenced with good effect, allowing propofol to be stopped. A total of three doses (0.5 mg/kg) of LMZ were administered 8 hr without adverse effects.

3.1.3. Case 3

A 15-year-old adolescent was admitted to our PICU after a 2 wk period of extracorporeal membrane oxygenation for staphylococcal pneumonia. Whilst on extracorporeal membrane oxygenation midazolam, lorazepam, triclofos, fentanyl, alimemazine, clonidine, morphine and haloperidol were all administered. Severe opioid and benzodiazepine withdrawal occurred and the patient remained combative and agitated as prolonged mechanical ventilation as required. LMZ was introduced at 25 mg/8 hr, after which all sedatives were slowly discontinued over the ensuing 5 days. LMZ was discontinued after 6 days with no side effects.

3.2. Patients with known severe behavioral disorders or autism (Table 1)

3.2.1. Case 4

A 5-year-old child with global developmental delay, autism and marked hospital phobia required PICU admission and mechanical ventilation following a ventricular septal defect repair. Remifentanyl, propofol (0.5 mg/kg/hr) and enteral clonidine (5 µg/kg/hr, 8-hourly) were titrated post-extubation to avoid accidental removal of central venous lines and chest drains. LMZ 12.5 mg (0.73 mg/kg) was started as the patient developed extreme anxiety post-extubation. The dose was optimized to 25 mg/8 hr, which achieved rapid control of the behavioral issues and agitation. The drug was weaned over 3 days on the cardiac ward with no side effects.

3.2.2. Case 5

A 9-year-old deaf autistic patient required prolonged postoperative immobilization following laryngotracheal reconstruction for subglottic stenosis. Risperidone and methylphenidate for attention deficit hyperactivity disorder were replaced with LMZ (0.25 mg/kg) 8 hr perioperatively. Initially morphine (60 µg/kg/hr) and clonidine (1 µg/kg/hr) were used for analgo-sedation during mechanical ventilation and later replaced with remifentanyl and propofol to facilitate extubation. In order to wean other sedatives, LMZ

Table 1
Demographic characteristics and sedation profile

Case no	Weight (kg)	Diagnosis	Co-morbidity	Analgesics or sedatives used	Maximum dose levomepromazine (mg/kg)	Duration of levomepromazine (hr)
1	8	Laryngotracheal reconstruction	Ex-premature	Morphine, clonidine, lorazepam	0.5	16
2	11	Aspiration pneumonia	Chronic lung disease	Morphine, clonidine, diazepam, propofol	0.5	16
3	66	Staphylococcal pneumonia	Post- extracorporeal membrane oxygenation	Morphine, clonidine, lorazepam, ketamine	0.4	149
4	17	Ventricular septal defect repair	Autism	Clonidine, remifentanyl, propofol	1.5	48
5	27	Laryngotracheal reconstruction	Autism	Morphine, conidine, lorazepam	1.9	416
6	50	Encephalopathy with seizures	None	Clonidine, midazolam, propofol	0.5	56
7	48	Spinal fixation with Halo traction	Klinefelter syndrome and autism	Morphine, propofol	0.8	118

was increased over 3 days up to 50 mg. The patient remained comfortable and manageable by medical staff on the wards as LMZ was weaned over a 2 wk period whilst risperidone and methylphenidate were re-introduced. LMZ was well tolerated throughout.

3.2.3. Case 6

A 13-year-old patient was ventilated for an acute febrile encephalopathy with seizures. Creatine phosphokinase (CPK) was elevated at 1423 IU/L. No infective or toxic cause was identified. The patient was extubated after 48 h but exhibited profound agitation with hallucinations despite midazolam (2 µg/kg/hr), propofol (2 mg/kg/hr) and enteral clonidine (100 µg/8 hr). LMZ 12.5 mg (0.25 mg/kg) was commenced and increased to 25 mg every 8 hr. This allowed rapid control of agitation, discontinuation of propofol and reduction in midazolam. After 12 h of LMZ, core temperature increased to 39 °C due to persisting shivering and inability to dissipate heat via sweating (a side effect of LMZ). An intravascular cooling device restored normothermia within 15 min and was stopped after 3 hr. Muscle rigidity was not present and CPK continued to decline (260 IU/L). Fever did not recur despite continuation of LMZ for a further 2 days. A full neurological recovery occurred over weeks, following immunomodulatory therapy with steroids and plasmapheresis.

3.2.4. Case 7

A 17-year-old teenager with Klinefelter syndrome, severe learning difficulties, aphasia, and autism

required spinal fixation for scoliosis and postoperative halo traction for spinal instability. LMZ was used in anticipation of a major challenge, given a previous history of difficult sedation. Morphine (40 µg/kg/hr) and propofol (1.5 mg/kg/hr) were weaned over 48 hr after 40 mg (0.85 mg/kg) of LMZ was administered prior to extubation. The addition of enteral clonidine (1 µg/kg/8 hr) together with LMZ achieved good behavioral control allowing the patient to be discharged to the surgical wards. LMZ was stopped after 3 days without adverse effects. Three months later, further orthopedic surgery was required and a similar regime was used with good effect.

4. Discussion

In patients with difficult sedation, the escalation of standard analgo-sedatives (usually opiates and benzodiazepines) can lead to drug tolerance, dependence, withdrawal and frequently polypharmacy with other adjunctive agents (e.g. ketamine, chloral hydrate, clonidine). These agents may have significant side effects including delirium, agitation, hallucinations, unfavorable hemodynamics and even death, as described e.g. in the propofol infusion syndrome [5–8]. We describe the successful use of LMZ as a strategy to manage difficult sedation by limiting prolonged high-dose opioid or benzodiazepine use and polypharmacy. LMZ has the advantage of avoiding respiratory depression [10] whilst being a potent sedative through its

action on non-opioid, non-benzodiazepine receptors. As with other neuroleptics avoidance of respiratory depression, especially when starting at low doses with gradual increases, compares favorably with traditional analgo-sedatives such as opioids or propofol. LMZ is an inexpensive agent that has antipsychotic, tranquilizing, and anxiolytic effects and is morphine-sparing [10]. It is non-addictive thus avoiding tolerance, dependence and withdrawal. Its successful use, via both enteral and IV routes, has been previously reported in critically ill children with refractory agitation despite haloperidol [11]. Similarly, we report success in critically ill children with difficult sedation.

We also describe the successful use of LMZ in anticipation of difficult sedation in patients with known behavioral problems including autism, who may otherwise require very high-dose conventional sedatives. We found a temporal association between the commencement of LMZ, and the resolution of anxiety, discomfort and agitation. Due to the long half-life of LMZ (approximately 20 hr), steady state plasma levels would only be achieved after 4 days at a constant dose and this lag time would be clinically unacceptable in this challenging group of patients. In order to achieve timely sedation control it was necessary in our strategy to rapidly escalate to adequate doses (0.25 to 1.8 mg/kg per dose) after ensuring that preceding lower doses were well tolerated.

Agitation or behavioral disturbances can also be the result of withdrawal syndrome [6]. We report on a patient (case 3) with suspected withdrawal syndrome, on whom commencement of LMZ brought about a defining turning point so that other sedatives could be discontinued. Further studies on the role of LMZ specifically for withdrawal syndrome are warranted.

Haloperidol or risperidone are typically administered for the treatment of delirium in pediatric intensive care, although these agents do have their limitations [12]. Our patients were not formally assessed for delirium but features that could be compatible with delirium were seen in cases 3, 4 and 6 and improved with LMZ. A potential role for LMZ in delirium has been previously reported [11] and our findings are consistent with this aforementioned success.

We did not observe side effects such as hypotension or hyperglycemia. Rarely agranulocytosis, cholestatic jaundice, or extrapyramidal adverse effects can occur [8] but these were not seen in our case series. Two patients developed fever during LMZ use, associated with their underlying diseases (cases 1 and 6). The

possibility of neuroleptic malignant syndrome warrants consideration as the prospects of early diagnosis, temperature control and supportive treatment reduce morbidity and mortality [13]. Case 6 developed severe hyperpyrexia probably due to the combination of shivering (heat generation) and lack of heat dissipation through LMZ-mediated antimuscarinic reduction in cutaneous sweating. Despite an underlying myositis, CPK remained low, muscle rigidity was not observed and rapid control of temperature was possible with an intravascular cooling device. The rapid resolution of pyrexia with supportive measures, despite continuation of LMZ, does not support a diagnosis of neuroleptic malignant syndrome.

We suggest a role for LMZ as a useful sedative in critically ill children where difficult sedation occurs and conventional agents are exhausted. Further studies are merited to examine its role in children with delirium, withdrawal syndrome, or those with known behavioral disorders who present a significant challenge to management in the critical care setting.

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