Evidence based opioid and benzodiazepine weaning following complicated Norwood palliation in an infant with hypoplastic left heart syndrome.

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Goals:

1. Discuss risk factors for opioid and benzodiazepine tolerance, dependence, and withdrawal in critically ill children
2. Discuss signs and symptoms of opioid and benzodiazepine withdrawal in pediatric patients, focusing on evidence based assessment tools
3. Discuss various evidence based opioid and benzodiazepine weaning strategies for pediatric patients
4. Discuss role of adjunct medications used in opioid and benzodiazepine weaning strategies
5. Discuss the importance of a formally organized pediatric pain service in the management of complex pain consults

Case Description:

The pediatric intensive care unit (ICU) consults the pediatric pain service regarding a 4-month-old male born at 37 weeks with hypoplastic left heart syndrome. The ICU team requests your help in the management of various classes of sedatives, hypnotics, and opioids that were started during his 4-month stay in the ICU as well as to outline a potential weaning strategy.

The child underwent a Norwood procedure on day of life 2, which was complicated by prolonged mechanical ventilation, renal dysfunction, and hemodynamic failure requiring venoarterial extracorporeal membrane oxygenation therapy. He is slowly recovering from his multisystem organ dysfunction and is almost ready for transfer out of the ICU. The plan is to

discharge him home for several months and then return for bidirectional Glenn cavopulmonary shunt.

The 4.2-kilogram child is currently on room air with normal vital signs, except for a SpO2 of 78%, which is his current baseline. His scheduled medications include methadone 0.5mg PO BID and lorazepam 1mg PO q6h. His breakthrough medications include methadone 0.5mg IV prn pain/agitation, lorazepam 1mg IV q6h prn agitation, fentanyl 15mcg q2h prn pain/agitation, and chloral hydrate 200mg PO prn agitation. He is intermittently fussy and inconsolable at times according to nursing staff.

Discussion:

Prolonged administration of intravenous opioids and benzodiazepines is commonly used to provide sedation and analgesia for critically ill children. However, the prolonged administration of these medications may result in tolerance and dependence, necessitating appropriate weaning of medications to avoid symptoms of withdrawal.

Knowledge of risk factors for the development of opioid and benzodiazepine withdrawal can help health care providers identify patients at risk in order to adjust their treatment plan accordingly. Risk factors for the development of opioid withdrawal include both the cumulative opioid dose and the duration of opioid exposure. The incidence of withdrawal is nearly 100% with a cumulative fentanyl exposure of 2.5mg/kg or exposure of 9 days (2). Another risk factor for the development of opioid withdrawal is the time course over which the weaning period occurs. Previous research has indicated that the development of withdrawal is more likely with rapid weans that occur over a 48-hour period (6). Weaning over a more prolonged time period is associated with a decreased incidence of withdrawal syndrome (3). The exact time course for a prolonged taper of opioid and benzodiazepines has varied in previous studies with improvement shown for weaning periods of at least 5 days up to 6 weeks. Another risk factor for opioid withdrawal in pediatric patients is the duration of extracorporeal membrane oxygenation therapy (7). Studies in adult intensive care unit patients also identify mechanical ventilation of 7 or more days, acute respiratory distress syndrome, use of neuromuscular blocking drugs, and propofol infusions for longer than 24 hours as risk factors for withdrawal syndrome (8). Specific risk factors for benzodiazepine withdrawal also include high cumulative dose, prolonged exposure, and too rapid tapering/abrupt cessation of the medication.

Cessation of opioid and benzodiazepine administration in children with complex and protracted hospital courses also requires an understanding of signs and symptoms of withdrawal. Often the clues to the occurrence of withdrawal are non-specific, hyperadrenergic responses that could also be associated with other derangements such as hypoxia, hypercarbia, psychosis, and metabolic abnormalities. The majority of signs and symptoms of withdrawal are manifested by central nervous system irritability, gastrointestinal dysfunction, and autonomic nervous system over activity. Some of the most common signs and symptoms include agitation, anxiety, muscle tension, sleeplessness, diarrhea, fever, sweating, and tachypnea.

Several clinical assessment tools are available to assist in the screening for withdrawal in the

pediatric population. One tool is the Neonatal Abstinence Score, which is designed as a nursing assessment specifically for neonates with in utero drug exposure. It assigns various points to certain signs and symptoms and then the cumulative score is used to indicate the severity of withdrawal. Another available tool is the Neonatal Narcotic Withdrawal Index. It is based on physician observations of several specific items and assigns a numerical value to the observations. Other scales that are available include the Opioid and Benzodiazepine Withdrawal Scale, the Sedation Withdrawal Scale, and the Sophia Benzodiazepine and Opioid Withdrawal Checklist. The Sophia Benzodiazepine and Opioid Withdrawal Checklist is a comprehensive list compiled of the 24 signs and symptoms of withdrawal documented throughout the pediatric literature.

It is key to have an armamentarium of evidence based weaning strategies to help prevent a withdrawal syndrome in pediatric patients at risk. Tapering of opioid medication doses is one important component in a weaning strategy. However, the length of the taper may vary depending on the cumulative dose and duration of exposure. Transition from IV to subcutaneous or oral medications provides another component in a weaning strategy. Various opioids including morphine, hydromorphone, and meperidine may be given subcutaneously. Methadone is also a popular agent used in the management of opioid withdrawal. Methadone provides advantages in that it is long acting, is available IV and PO with excellent oral bioavailability, and can provide a beneficial switch from one class of opioids to another. Several weaning protocols have been suggested which convert opioid infusion doses to equipotent enteral methadone doses (conversion range: 1 mcg/kg/hr Fentanyl = 0.2-0.4 mg/kg/day enteral methadone). When converting from one opioid class to another, particularly when methadone is used, one should consider reducing the initial calculated conversion dose by 30-50% to provide a receptor cross tolerance safety margin. Lorazepam is a commonly used agent for benzodiazepine withdrawal that may be given enterally. Once conversion to enteral medications such as methadone and lorazepam has occurred, these medications may then be tapered by 10-20% of the initial dose every 1-2 days pending the result of serial clinical assessments. In addition to medications, efforts to promote gentle handling of patients and reduction in environmental stimulation are important in the management of withdrawal. Other important considerations in developing a weaning strategy include the length of weaning. Several studies have shown a decreased incidence of withdrawal symptoms when weaning occurs over several weeks (3). The safety of shorter weaning time periods such as 48 hours is questioned (6). However, in a prospectively randomized, double blind trial, Berens et al found that opioid dependent patients may be weaned just as successfully with enteral methadone over a 5 day period as with a 10 day period (2). Some patients who are exposed to multiple agents in multiple classes for several weeks may benefit from weaning a single class of agent at a time. Given favorable family dynamics and close follow-up, it may occasionally be feasible to complete weaning strategies after discharge from the hospital on an outpatient basis.

Adjunctive medications may also be useful components in weaning strategies for opioid and benzodiazepine dependent patients. Methadone and Lorazepam are some of the more commonly used agents, however the utilization of adjunctive medications may be beneficial at times. Adjunctive medications include clonidine, barbiturates, chlorpromazine, diazepam,

chloral hydrate, and buprenorphine. Clonidine, as an alpha 2-receptor agonist, activates the same potassium channel as μ-opioid receptors via a different G-protein allowing a reduction in opioid dose while minimizing withdrawal symptoms. Knowledge and experience with these adjunctive agents is important and argues that utility of a formally organized pediatric pain service is key in the management of more complex regimens.

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