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The Impact of Pharmacovigilance-Based Insights in Pediatric Intensive Care Unit (PICU): *A perspective from critical care pharmacy practice*

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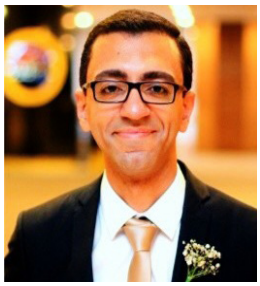

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He is a community and clinical pharmacist with +15 yrs of experience as a pharmacist with excellent analytical, and communication skills for interaction with patients. As an instructor as well as a medical advisor, he has a natural passion for clinical sciences and diversified abilities to fully master therapeutic and research areas with an outstanding medical background, extensive patient-oriented expertise, and strong business acumen.

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One of the emerging challenges in critical care pharmacy practice is the implementation of pharmacovigilance with drugs administered in the intensive care unit. Although the role of intensivists is the main pillar for such a significant topic, but the role of critical care pharmacists is a game changer in terms of advancing the practice of administering drugs to critically ill patient age category, i.e. pediatric patients.

Seriously ill pediatric patients admitted to Pediatric Intensive Care Unit (PICU) for treatment and supportive therapy require both sedation and analgesia to maintain comfort and provide pain relief that is associated with mechanical ventilation, invasive procedures, prevention of distress from the presence of unfamiliar personnel and from the high level of background noise, which can disturb sleeping patterns and the need to stay calm, i.e. lie relatively still. The level of sedation of post-operative infants has been shown to impact on subsequent morbidity, and even mortality. Undersedation and oversedation are both harmful.

In critical and intensive care, inadequate sedation and agitation have been correlated with adverse short- and longer-term outcomes. On the other hand, oversedation delays recovery, promotes drug tolerance and leads to withdrawal symptoms of the drugs such as agitation, seizures, psychosis, hallucinations, tachycardia and fever. Undersedation is unacceptable in a vulnerable child: the child may 'fight' the ventilator leading to accidental extubation, adverse hemodynamic responses, insufficient gas exchange or the loss of invasive access or monitors. The evidence-based data of randomized controlled trials (RCTs) in this area is small and the SLEEPS (Safety profile, Efficacy and Equivalence in Pediatric intensive care Sedation) trial was planned to compare the off-label use of both midazolam and clonidine, two sedatives widely used within Pediatric Intensive Care Units (PICUs). A dossier summarizing the safety profiles of both drugs is requested by the Medicines and Healthcare products Regulatory Agency (MHRA) to grant the application to obtain a Clinical Trials Authorization.

The SLEEPS trial is a UK multicenter, double-blind, randomized equivalence trial to determine whether or not intravenous clonidine can produce equivalent controlled sedation in the critically ill child when compared with intravenous midazolam, i.e. intravenous (i.v.) clonidine as an alternative to i.v. midazolam. Participants were children (30 days to 15 years inclusive) weighing ≤ 50 kg, expected to require ventilation on PICU for > 12 hours.

Midazolam was administered as, 200 µg/kg loading dose then 0–200 µg/kg/hour, versus clonidine, 3 µg/kg loading dose then 0–3 µg/kg/hour. Both groups also received opioid, morphine.

Medline was searched to identify randomized controlled trials, observational studies, case reports and series. 288 abstracts were identified for midazolam and 16 for clonidine with full texts obtained for 80 and 6 articles respectively.

Randomized Controlled Trials (RCTs), Controlled Clinical Trials (CCTs), observational studies and case reports or case series are included. Only studies assessing the safety of continuous intravenous infusion of midazolam or clonidine when used as sedative for mechanically ventilated children < 18 years old.

This age limit was set to allow variability in definition of pediatric population.

Only studies administering midazolam or clonidine either as monotherapy or concomitantly with opioid are selected to reflect routine clinical practice. Studies assessing the use of midazolam or clonidine via any route other than a continuous intravenous infusion are excluded.

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Non-inferiority of clonidine to midazolam was established. The proportion of children who were adequately sedated for ≥ 80% of the time was 21 of 61 (34.4%)–clonidine, and 18 of 59 (30.5%)–midazolam. Thirty-three studies provided data for midazolam and two for clonidine. The majority of data has come from observational studies and case reports. The MHRA provided details of 10 and 3 reports of suspected adverse drug reactions. The decision to collect all adverse event data or restrict collection should be determined by a risk assessment for the trial and consider how well established the risk/benefit profile of the medicines under study are, licensing status of the drugs and current level of clinical use.

Cardiovascular adverse effects monitoring was: Five randomized controlled trials (RCTs) actively monitored cardiovascular adverse effects of midazolam. Neurological adverse effects monitoring was: Three RCTs actively monitored patients for neurological complications while receiving midazolam. Prolonged sedation: one RCT and two prospective cohort studies actively monitored children for prolonged sedation after discontinuation of midazolam infusion.

Metabolic/endocrine: One cohort study prospectively assessed children receiving midazolam for altered hypothalamic-pituitary-adrenal axis function, and the authors clearly describe the cortisol stimulation test used. One study retrospectively assessed patients for metabolic acidosis and hyperlipidemia. This was done to assess the safety of propofol rather than midazolam.

Withdrawal and behavioral: Withdrawal from midazolam was not monitored or reported in any of the 7 RCTs.

Six prospective cohort studies report possible withdrawal symptoms after continuous infusion with midazolam and all were considered to be adverse drug reactions (ADRs).

Sheridan reports that one child suffered withdrawal symptoms following discontinuation of midazolam. These symptoms consisted of vomiting, tremulousness and sweating. Hughes reports that 8/53 children in their study had ‘abnormal behavior’ after discontinuing midazolam therapy. Three patients had visual hallucinations (one of these also had auditory hallucinations), three were ‘clearly disorientated’ and two patients did not recognize their parents, had ‘puppet-like’ movements and ‘laughed inappropriately’.

Four case series and five case reports described symptoms that were attributed by the authors to benzodiazepine withdrawal. The symptoms reported included irritability, agitation, restlessness or inconsolability, abnormal movements (choreoathetoid or non-purposeful, seizures, ‘vigorous limb movements’, orofacial abnormal movements and myoclonic jerks), hallucinations, grimacing, ‘jitteriness’, clonus, disorientation or abnormal communicative skills, blindness, abnormal behavior, hyperactivity and aggression vomiting, diarrhea, poor feeding, hypertension and tachycardia, and yawning.

The risk assessment for the SLEEPS trial was also informed by a systematic review which did not identify any additional safety concerns to those specified within the existing Summary of Product Characteristics therefore a decision was made to restrict data collection to adverse reactions.

The Summary of Product Characteristics (SmPCs) of the UK Electronic Medicines Compendium (EMC) were obtained for each sedative. As the conditions of use of both midazolam and clonidine in the clinical trial are not the same as those licensed, the Clinical Trials Authorization application to the Medicines and Healthcare products Regulatory Agency (MHRA) requested that the Summary of Product Characteristics (SmPCs) for its licensed use be complemented with a summary of the relevant data supporting its use in the currently proposed clinical study.

The conclusion of such trial, in terms of pharmacovigilance aspects, was no adverse reactions were identified in addition to those specified within the SmPCs for the licensed use of the drugs. Based on this information and the wide spread use of both sedatives in routine practice the pharmacovigilance plan was restricted to adverse reactions.

Unsurprisingly, it is not just about those adverse reactions listed in the SmPCs, but actually, any drug could be a potential cause of serious adverse reactions. For example, the Stevens - Johnson syndrome (SJS), which is-according to Mayo Clinic definition- “*a rare medical emergency, and serious disorder of the skin and mucous membranes that requires hospitalization*” could be overwhelming in PICU patients.

Although our examples here, midazolam as well as clonidine, are not a well-known precipitants of Stevens - Johnson syndrome (SJS), but recently, the role of critical care and hospital pharmacy practice is a game changer.

Pharmaceutical researches demonstrated that Quantitative Structure-Activity Relationship (QSAR) models can accurately identify SJS active and inactive drugs. Requiring chemical structures only, QSAR models provide effective computational means to determine potentially harmful drugs for subsequent targeted surveillance and pharmacoepidemiologic investigations.

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