Pethidine-related neurotoxicity in pediatric sickle cell disease: a systematic review

Khalid Ali Almasoud¹, Atheer Fahad Aldaghmi², Amna Ali Alahmaed², Mansour Mana Alzamanan¹*, Ali Hussain Majrashi¹

ABSTRACT

Sickle cell disease describes a set of related blood disorders that result from defective production of hemoglobin that causes rigid fibers to form in the red blood cells, bending them into a characteristic sickle shape. These misshapen blood cells are then prone to becoming lodged in smaller blood vessels, resulting in a vaso-occlusive crisis, which can be very painful. Rapid and potent analgesia is crucial in the care of patients presenting with sickle cell crisis, and opioid analgesics, such as pethidine and morphine, have been the mainstay of treatment for decades. However, there are reports in the literature of seizures associated with pethidine use, particularly if used for more than a few days or in patients with kidney disease. A systematic review of the literature was conducted to identify any case reports or studies of the use of pethidine in children presenting with painful sickle cell crisis with a specific focus on the prevalence of seizures in this patient group. The pharmacology and pharmacokinetics of pethidine and its active metabolite norpethidine are briefly explored, along with alternative analgesic approaches, both pharmacological and nonpharmacological.

Keywords: Pethidine, neurotoxicity, sickle cell disease, pediatric, systematic review.

Introduction

Sickle cell disease

Sickle cell disease results in alteration of the normal red blood cell morphology, producing inflexible sickle-shaped red blood cells that result in a plethora of vascular difficulties, typically as a result of occlusion, and affects more than four million people globally [1]. The range of blood disorders that produce sickle cell disease are the result of autosomal recessive mutations inherited from both parents. Standard hemoglobin A (HbA) is formed of two alpha and two beta chains. This becomes malformed as a result of a single nucleotide polymorphism in the beta-globin gene that produces a single amino acid substitution (valine in the place of glutamate at position six), giving rise to hemoglobin S (HbS). Under conditions of normal oxygenation, HbS behaves in the same manner as HbA; however, under hypoxic conditions, HbS units polymerize, forming insoluble fibers that cause deformation of the blood cell. Moreover, sickle cell disease is associated with greater extracellular levels of hemoglobin, specifically, HbS, likely as a result of erythrocyte damage, and HbS has been shown to activate platelets, which likely plays a role in the intravascular clot formation often seen in patients with sickle cell disease [2]. As many of the capillaries that perfuse the tissues of the body have internal diameters around the same size as a red blood cell, with some even smaller that require the cells to squeeze out of shape to pass through, any rigidity or deformation in erythrocyte morphology can lead to blockages. This can produce vaso-occlusive crisis, splenic sequestration crisis, acute chest syndrome, aplastic crisis, hemolytic crisis, and a range of other complications that all need prompt management to ensure the best outcome [3].

As a genetic disorder of the blood, sickle cell disease often presents initially in early childhood. HbA is not formed in utero or neonates, with the body instead using hemoglobin F (HbF) for the first few months of life, after which HbA becomes the dominant form. HbF, lacking the beta subunits, is not affected by the sickle cell mutations [4]. Although symptoms do not generally appear in the neonate, routine screening of pregnant women can identify fetuses likely to develop the condition.
Treatment of sickle cell disease focuses largely on controlling the symptoms and attempting to reduce the risk of complications, rather than treating the underlying cause. Having said that, bone marrow transplants may be successful in curing the condition, although obtaining specific donor matches can be challenging [5]. Advances in this area using gene editing have the potential to offer wider access to curative treatments for sickle cell disease [6,7]. Current standard treatments involve prophylactic antibiotics, folic acid, blood transfusions, psychological therapies, and hydroxyurea [8-10]. These treatments aim to reduce the risk of infection, increase the population of healthy red blood cells, and in the case of hydroxyurea reactivate the production of fetal HbF in adult cells [11-13].

One of the most obvious of the signs and symptoms associated with sickle cell disease is the crisis. These attacks of extreme pain that result from a range of underlying mechanisms and are often brought on by infection, dehydration, or acidosis, although many incidences have no identifiable cause [14]. Vaso-occlusive events produce tissue ischaemia which results in both acute and chronic pain along with the potential for organ damage that can affect virtually any part of the body. Splenic sequestration is another common crisis as the spleen swells, becoming engorged with misshapen blood cells; splenic infarction and loss of function can occur in early childhood in untreated patients [15].

Any of these events can be profoundly painful, requiring prompt and effective analgesic therapy. Opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are the treatments of choice, and pethidine has been used with some degree of success in these cases. However, there have been reports of adverse neurological reactions to pethidine treatment, specifically the development of seizure episodes [16].

**Pethidine**

Also known as meperidine, pethidine is a synthetic opiate that was first synthesized in the late 1930s; while first generated as a potential anticholinergic agent, its analgesic properties were discovered soon afterward [17]. It is used for moderate to severe pain, and remains commonly prescribed during labor, but has been largely replaced with other opiates on account of its interaction profile and adverse effects. Similarly, it is no longer recommended for the pain of sickle cell crisis, with codeine, morphine, or diamorphine being recommended in its place [18]. Pethidine exerts its effects through several mechanisms of action. Its primary action is as an agonist at the μ-opioid receptor, which is distributed throughout several regions of the brain and reduces the perception of pain while inducing drowsiness. Its interactions with sodium channels produce local anesthetic effects, and it has been shown to inhibit the dopamine transporter and norepinephrine transporter similarly to cocaine [19]. Pethidine hydrolyses quickly into pethidinic acid via the action of hepatic carboxylesterase, but it is also subject to demethylation via several cytochrome oxidases to produce norpethidine, which also exhibits some analgesic activity albeit with a significantly longer elimination half-life, subsequently being glucuronidated in the liver and eliminated via the kidneys. The half-life of pethidine is in the region of 2-4 hours, whereas the half-life of norpethidine is closer to 8-12 hours. This causes norpethidine to accumulate if repeated doses of pethidine are given or if the excretion of norpethidine is compromised, such as in renal insufficiency. These reactions are illustrated in Figure 1.

Pethidine is contraindicated in patients with a history of seizures or renal failure, so pethidine should not be used to treat the pain of sickle cell crisis in patients with such histories. In fact, some institutions have restricted its use in pediatric patients because there are acceptable alternatives for every indication [20]. This review aims to determine the mechanisms of neurotoxicity of pethidine in pediatric patients suffering from sickle cell crises, while also exploring the prevalence of such cases.

**Methods**

To construct a focused review, it is necessary to define the population and interventions being studied, along with suitable comparisons and clear outcomes [population, intervention, comparison, and outcome (PICO)]. In essence, this review sought data on the neurotoxic side effects of pethidine in pediatric patients presenting with painful sickle cell crises. The PICO parameters are summarised in Table 1.

To identify papers suitable for analysis, ScienceDirect, MEDLINE (via PubMed), the Public Library of Science (PLoS), and the Cochrane CENTRAL database of clinical trials were examined using the basic search terms, “pethidine,” “sickle,” and “seizure,” using filters...
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Table 1. PICO parameters used in the construction of the literature review.

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients under 16 years with painful sickle cell crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Pethidine (meperidine) for pain management</td>
</tr>
<tr>
<td>Comparison</td>
<td>Other analgesic treatments including pharmacological and nonpharmacological options</td>
</tr>
<tr>
<td>Outcome</td>
<td>Seizures</td>
</tr>
</tbody>
</table>

Table 2. Search terms and filters applied to the various databases examined, along with the number of initial hits.

<table>
<thead>
<tr>
<th>Search terms and filters</th>
<th>Database</th>
<th>Initial number of hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine sickle seizure</td>
<td>MEDLINE (via PubMed)</td>
<td>7</td>
</tr>
<tr>
<td>Pethidine sickle seizure</td>
<td>ScienceDirect</td>
<td>39</td>
</tr>
<tr>
<td>• Research articles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Case Reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine sickle seizure</td>
<td>Public Library of Science</td>
<td>100</td>
</tr>
<tr>
<td>• Research articles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pethidine sickle seizure</td>
<td>Cochrane CENTRAL</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Inclusion and exclusion criteria used to refine the literature search.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials, case reports, and case series</td>
<td>Systematic reviews or meta-analyses</td>
</tr>
<tr>
<td>Reports involving children under 16 years</td>
<td>Reports involving adults</td>
</tr>
<tr>
<td>Pethidine for treatment of sickle cell pain crisis</td>
<td>Treatments other than pethidine, or conditions other than pain crisis in sickle cell disease</td>
</tr>
</tbody>
</table>

to identify primary research and case reports where possible. This search strategy is summarised in Table 2.

To ensure the systematic review maintains a clear focus, inclusion and exclusion criteria were applied during the process of filtering the literature. Primary research papers were selected for inclusion, along with case reports and case series. In each instance, these must include the treatment of painful sickle cell crisis in children below the age of 16 with pethidine. Reports that involved adults or treatments other than pethidine were excluded, as were any secondary studies such as systematic reviews and meta-analyses. These criteria are summarised in Table 3.

Results

The progression of literature through the search and selection process is illustrated in Figure 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22], and screenshots of the initial searches are shown in Appendix 1.

The first of the studies selected for inclusion in the systematic review was presented by Pegelow [23]. The study took the form of a questionnaire that was sent to clinical researchers in sickle cell disease to explore their experiences of pain management in children. Of the 21 respondents, 20 routinely used parenteral opioid analgesics in their patients, with 11 opting for pethidine. Nine respondents reported pethidine-associated convulsions, five of whom delivered the drug intravenously, three by intramuscular injection, and one preferred to give pethidine orally. Despite their experience with convulsions, six of these respondents continued the use of pethidine as first-line treatment. The second study was presented by Woolard and Terndrup [24], in which a retrospective review of the medical records of 759 children below the age of 16 presenting to the emergency department requiring sedative-analgesic agents. This included children presenting with a range of issues that included trauma such as fractures, lacerations, head injuries, and others, along with nontrauma presentations such as seizures, infections, and sickle cell crisis. The authors report one reaction that they describe as paradoxical in which a patient given pethidine and promethazine experienced a seizure, but this was not a patient with sickle cell disease (they had presented with a laceration).

The third and final study selected for inclusion was presented by Nadvi et al. [25], in which a retrospective analysis of the incidence of pethidine-associated seizures was carried out in a large group of patients with sickle cell anemia, the majority of whom were pediatric patients. A total of 510 patients with ages ranging between 2 days and 31 years were included, comprising 2,921 hospital admissions for vaso-occlusive episodes. Seven patients experienced seizures, representing 1.4% of patients and 0.24% of hospital admissions. In five of these cases, a nonsickle cell disease-related cause was identified, leaving only two cases in which pethidine was potentially...
implicated, accounting for 0.4% of patients (0.06% of hospital admissions). These two 16-year-old female patients exhibited generalized tonic-clonic seizure episodes with electroencephalogram (EEG) indicating either generalized or focal spike waves; these patients had received pethidine for several days. The others were four patients who exhibited seizures (aged 18 years, 2 weeks, 2 days, and 2 months) and had received no pethidine but had a history of skull fracture, stroke, hydrocephalus, or febrile seizure, and the fifth patient was a 17-year-old male whose EEG, computed tomography (CT), and magnetic resonance imaging (MRI) scans were normal, leading the authors to describe his episode as “probable hysteria” [24].

Discussion

The academic literature contains several case reports and case series that explore the occurrence of seizures secondary to pethidine in a variety of usage situations, but larger studies or reviews that focus on seizures in children receiving pethidine for sickle cell pain crisis are rare. This systematic review identified only three studies that satisfied the inclusion and exclusion criteria, at least in part. In the earliest study, published in 1992, nearly half of the respondents noted seizures in pediatric patients treated with pethidine for sickle cell crisis, although they often continued to prescribe the drug. While the study provided no data on the number of incidents, the continued use of pethidine suggests that it was the experience of clinicians that seizures were encountered only rarely. The second study, published in 1994, reviewed records of over 750 children who presented with various painful conditions. The single seizure event reported was not related to sickle cell disease and occurred in a patient prescribed both pethidine and promethazine. The third study, published in 1999, assessed over 500 patients and identified only two events of pethidine-associated seizure. Three other cases of pethidine-associated seizures involving adults were reported by Hermes and Hare [21], and their subsequent literature review also revealed that, just as in their patients, those most at risk of seizures were the patients receiving pethidine against a

Appendix 1. PRISMA flowchart illustrating the progression of literature through the search and filtering process. Flowchart adapted from Page et al. [22].
background of renal impairments, including patients with sickle cell anemia in whom renal impairment is more likely. This is in keeping with previous observations of the increased toxicity of the norpethidine metabolite, and its subsequent accumulation in renal impairment, rather than pethidine itself.

Norpethidine

The rate at which pethidine is converted into norpethidine is governed by the activity of three of the cytochrome p450 enzymes, CYP2B6, CYP2C19, and CYP3A4, which can vary in their levels between individuals and can be influenced by other factors including hepatic health and the presence of other medication [26]. Irrespective of this, the simple nature of the difference in half-lives between pethidine and norpethidine will lead to the accumulation of the latter whenever multiple doses of the former are given.

Norpethidine has been associated with anxiety and tremors, but can also induce myoclonus and generalized seizures following the administration of large doses of pethidine over several days, and is correlated with patients with renal impairment [27]. Co-administration of enzyme-inducing drugs such as phenobarbital or a history of seizures increase the risk of seizure episodes with pethidine usage, but renal impairment places patients at a particularly increased risk. However, Ballas [27] makes the point that when patients receiving pethidine experience seizures, they are automatically attributed to norpethidine despite there being various other potential causes of seizures in sickle cell patients, including cerebrovascular complications such as stroke that require rapid diagnosis and management. Indeed, Nadvi et al. [25] initially noted seven seizure incidents, yet were able to assign causes other than pethidine to five of these patients, i.e., stroke, skull fracture, hydrocephalus, and a febrile convulsion [25].

A recent narrative review that explored several studies on pain management in sickle cell disease identified four studies that made use of pethidine, none of which reported seizures [28]. Similarly, a review presented by Schlick et al. [29] reported a broad examination of the literature in which 66 articles were identified, only 33 of which had primary clinical data on pethidine-associated seizures, which altogether reported incidence in 50 patients. Twenty of those events were considered likely to be seizures, four events were unlikely to have been seizures, and 26 events were indeterminate. The presence of comorbidities in these patients confounds analysis somewhat, but the conclusion presented by the authors was that the evidence base for pethidine-induced seizures in humans is limited, and the risk of seizures with pethidine administration may be overstated. The majority of the identified articles were published in case report form, with only two studies involving pethidine in sickle cell crisis, which are discussed briefly here.

One of the studies identified by Schlick et al. [29] involved a prospective observational study of 14 adult patients prescribed intramuscular pethidine in which pethidine and norpethidine levels were to be recorded and any correlation with seizure episodes to be analyzed [30]. Although they recorded seizure episodes, there was no association between peak plasma pethidine concentrations and those seizures, although the authors go on to recommend that daily doses exceeding 25 mg/kg are likely to induce neuroexcitatory effects due to the accumulation of norpethidine.

The other study identified by Schlick et al. [29] was presented by Nadvi et al. [25] and was identified during the systematic literature review presented here, with seizures attributable to pethidine occurring in around 0.4% of patients and accounting for 0.06% of hospital admissions, suggesting that the risk of seizures should not dissuade clinicians from prescribing pethidine.

Limitations of the systematic review

The methodological process of conducting systematic reviews aims to bring together multiple examples of high-quality research so that trends in the data may be identified and analyzed, providing up-to-date information and guidance. However, while a subject of considerable importance, the academic literature is largely devoid of recent information regarding the use of pethidine in the management of pain associated with sickle cell crisis, mostly as a result of guidance from the National Institute of Health and Care Excellence (NICE) dated 2012 states “Do not offer pethidine for treating pain in an acute painful sickle cell episode” [31]. Consequently, the studies and cases retrieved in the presented review date back decades, with the most recent included paper published in 1999 [25].

Alternative analgesia

As with the prescription and administration of any medicine, healthcare professionals are under ethical obligations to provide safe treatment. Consequently, if there is a concern that a particular medication may present unnecessary risks, it is reasonable to seek alternative strategies. Moreover, rather than using the same approach for all patients, recent research has demonstrated that an individualized pain plan can result in decreased pain scores and decreased days on breakthrough opiates [32,33]. Several other opioid analgesics are available, and even as far back as 1990 they were being considered against pethidine for the treatment of painful episodes in children with sickle cell disease; nalbuphine, for example, demonstrates equivalent efficacy with pethidine [34]. There is also the consideration of the method and timing of drug delivery, which has been shown to make a substantial difference in pain scores. A study that directly compared two analgesic regimens that consisted of pethidine, morphine, or codeine bolus every three to four hours, or a continuous infusion of morphine; no adverse effects were present in either group, and the continuous
infusion produced better analgesia than the intermittent treatment [35].

Given that vaso-occlusive pain can have a neuropathic component, a phase II randomized double-blinded placebo-controlled study into the use of gabapentin for acute pain in sickle cell crisis was recently reported [36,37]. Interestingly, although there was no significant difference in the overall pain reduction with the introduction of gabapentin, a specific subset of patients experienced a significant reduction in pain scores.

These were the patients presenting with the more severe genotype, HbSS, during acute crisis. Larger prospective studies were recommended by the authors.

Nonpharmacological treatments for pain should also be considered in patients presenting with vaso-occlusive crises. Psychological therapies including cognitive-behavioral therapy (CBT) shown to be an effective aid in the management of chronic pain, and can reduce psychological distress and increase the confidence of afflicted children [38]. Children who were included in a yoga program while hospitalized for vaso-occlusive crisis showed significantly reduced pain scores after only one session [39]. However, there were no significant differences between those patients and control patients undergoing standard treatment in terms of their levels of anxiety, length of hospital stay, or opiate use. Similarly, an acupuncture intervention was investigated as an alternative approach to pain management in children with sickle cell disease, which demonstrated decreased pain for those undergoing the treatment with no adverse event reported [40]. A broad range of nonpharmacological treatments are used by patients and their families to manage pain during sickle cell crisis, and the impact of many of these interventions remains to be thoroughly explored, including guided imagery, virtual reality, prayer, massage, distractions, and alterations of fluid intake [41].

Current guidance from the National Institute for Health and Care Excellence (NICE) covering the management of acute painful sickle cell episodes in children, young people, and adults who present at the hospital recommends an individualized assessment at the initial presentation [31]. The guidelines suggest a weak opioid analgesic for those with moderate pain who have not yet had any other analgesia, and that all patients should be offered regular paracetamol and NSAIDs unless contraindicated. As mentioned previously, the NICE guidelines explicitly state “Do not offer pethidine for treating pain in an acute painful sickle cell episode.”

A recent review of clinical trials of recently approved drugs for sickle cell disease found several drugs, including L-glutamine, voxelotor, and crizanlizumab, that were well tolerated and reduced the number of sickle cell crisis episodes, and were effective alone and in combination with hydroxyurea [42]. The focus of recent research into the management of sickle cell disease is the reduction of occurrences of vaso-occlusive crisis, with several promising treatments that specifically target the pathophysiological processes involved in cell adhesion and inflammation [43]. Other emerging treatments for sickle cell disease include allogeneic stem cell transplant [44], mRNA treatments [45], and gene editing [46].

**Conclusion**

Pethidine was the drug of choice for vaso-occlusive episodes for decades, but the neurotoxic metabolite norpethidine is known to accumulate in the body due to its significantly longer half-life relative to the parent compound. While several examples of norpethidine-induced seizures are reported in the literature, particularly when used in conjunction with other drugs or in patients with renal insufficiency, the seizure risk has likely been overstated when reports are put in the context of the many patients who are treated without incident, with an incidence estimated at 0.4% of pethidine-treated children. Having said that, pethidine has largely been replaced, with NICE guidelines stipulating that it should not be used in sickle cell crisis, and other opiates are now selected preferentially. Ongoing research has identified other pain treatment strategies, both pharmacological and nonpharmacological, that are effective and well-tolerated, and research into the management and treatment of the underlying disease continues.

**List of Abbreviations**

HbA Hemoglobin A
PICO Population, intervention, comparison, and outcome

**Conflict of interest**

Not applicable.

**Funding**

None.

**Consent to participate**

Not applicable.

**Ethical approval**

Not applicable.

**Author details**

Khalid Ali Almasoud1, Ather Fahad Aldaghmi2, Amna Ali Alahmaed2, Mansour Mana Alzamanan1, Ali Hussain Majrashi1

1. Pediatric Emergency Department, Maternity and Children Hospital, Dammam, Saudi Arabia
2. Pediatric Department, Maternity and Children Hospital, Dammam, Saudi Arabia

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