Seizures and Meperidine: Overstated and Underutilized

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Meperidine is used for pain control and treatment of shivering. Concerns about neurotoxicity, particularly seizures, have led to efforts limiting meperidine use. We reviewed the body of evidence linking meperidine to seizures. We searched PubMed for the terms meperidine, normeperidine, pethidine, and norpethidine; each was combined with the terms: seizure, epilepsy, epileptogenic, toxicity, overdose, seizure threshold, and convulsion. Articles were assessed for relevance. Semiologies were reviewed to ascertain seizure likelihood. Our search yielded 351 articles, of which 66 were relevant. Of these, 33 had primary clinical data on meperidine-associated seizures, comprising 50 patients. Twenty events were deemed likely to be seizures, 26 indeterminate, and 4 unlikely. Most studies were case reports. Confounding comorbidities were frequent. The evidence base for meperidine-associated seizures in man is scant. Seizure risk associated with meperidine appears to be overstated. The utility of meperidine should continue to be explored, especially for therapeutic hypothermia.

Background

MEPERIDINE (ALSO KNOWN AS PETHIDINE) is a synthetic opioid analgesic. While its use as an analgesic has declined markedly in recent years (Hastie *et al.*, 2014), it is commonly used as treatment against shivering in accidental and induced hypothermia. Alternate opioids have demonstrated similar or even superior analgesic efficacy when compared with meperidine (Plummer *et al.*, 1997). Various guidelines for pain management exclude meperidine as part of their treatment algorithms (American Society of Anesthesiologists Task Force on Acute Pain, 2004); others specifically recommend against meperidine use for pain treatment (Swarm *et al.*, 2010). These recommendations, in part, stem from the reported risk of seizures in association with meperidine (Gutstein and Akil, 2006). While there are superior opioid analgesics commonly available to treat pain, meperidine has become a mainstay in many antishivering protocols. It lowers the shivering threshold more potently than other opioids (Kurz *et al.*, 1997), an effect that is enhanced by other agents, notably buspirone (Mokhtarani *et al.*, 2001). The antishivering effect of meperidine has been exploited in studies of therapeutic hypothermia (Hemmen *et al.*, 2010) as well as in clinical practice (Polderman and Herold, 2009). Concerns regarding potential toxicity, especially seizures, continue to create hesitation in using meperidine. We sought to review the body of evidence available that links meperidine to seizure risk.

Methods

Search strategy

We performed a PubMed search for the terms meperidine, normeperidine, pethidine, and norpethidine; each search term was combined with the terms: seizure, epilepsy, epileptogenic, toxicity, overdose, seizure threshold, and convulsion. The final updated search occurred on August 1, 2014. The abstract and title for each article were read, and the likelihood of the article containing information relevant to the association between meperidine and seizures was judged. If the abstract was not available, the article in its entirety was retrieved and reviewed. Articles were considered relevant if they contained original data associating meperidine or normeperidine with seizure activity. Articles that referred to previously published cases were segregated.

Relevance of articles

Each article was classified as either relevant, likely relevant, possibly relevant, likely irrelevant, or irrelevant. Of these, the likely irrelevant and irrelevant articles were discarded. Studies classified as possibly relevant were then reviewed in entirety and subsequently reassigned as relevant or irrelevant. The remaining articles were reviewed and further classified as either preclinical (pertaining to animal or basic science studies) or clinical (involving human subjects) studies.

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Seizure descriptions

The cases of meperidine-associated seizures from the clinical studies were abstracted in table format and analyzed. Seizure descriptions were reviewed and events classified as likely (clinical semiology consistent with seizure, followed by postictal state, or electrographic seizure as captured on an electroencephalogram [EEG]), unlikely (clinical description not compelling for seizure or alternate diagnosis given), or indeterminate (insufficient information provided to categorize the symptom as seizure).

Results

Using the search terms specified, we obtained a total of 351 individual article abstracts. Relevance of articles was determined based on whether they presented original data or index cases relating seizures to meperidine use. Of these 351 abstracts, 46 were classified as relevant, 23 as probably relevant, 39 as possibly relevant, 28 as probably irrelevant, and 215 as irrelevant. After detailed review of the entire article of each of the 39 possibly relevant, we found 66 articles containing primary data relating seizures to meperidine use. Of these, 33 were clinical (involving human subjects and clinical data) and 33 were preclinical. We reviewed the data from the clinical articles and the information from these was abstracted (Table 1).

The 33 identified clinically relevant studies contained a total of 50 patients who experienced clinical seizures in the context of meperidine use. Of these, 12 patients were below the age of 18. The majority of these seizures were published in case report form; one study was a prospective study of meperidine and normeperidine levels in 14 sickle cell crisis patients (Pryle *et al.*, 1992), one was a cohort study of 14 patients with either renal failure or cancer comparing meperidine and normeperidine levels in those groups (Szeto *et al.*, 1977), one was a chart review of patients at a single institution at high risk for drug toxicity (Seifert and Kennedy, 2004), one a retrospective study of 67 cancer patients examining excitatory effects of meperidine and their association between meperidine/normeperidine levels (Kaiko *et al.*, 1983), and one a retrospective review of meperidine-associated seizures in a large population of pediatric sickle cell patients (Nadvi *et al.*, 1999).

Meperidine was most frequently administered intravenously in 20 cases, intramuscularly in 14 cases, orally in 3 cases, and intrathecally in 1 case. Six patients received meperidine through multiple routes of administration, and in six cases, the route of administration was not reported. A wide range of meperidine doses was reported, from as little as a single dose of 25 mg IV (Ozkaya *et al.*, 2012) to 1500 mg IV in 12 hours (Knight *et al.*, 2000). Patient-controlled analgesia was used in 15 patients.

TABLE 1. ADULT CASES OF MEPERIDINE-ASSOCIATED SEIZURES

Author/year	No. of pts	EEG?	Imaging?	Seizure likelihood	Confounders
Szeto <i>et al.</i> (1977)	2	No × 2	No × 2	Indeterminate, unlikely	(1) Bone cancer, (2) s/p renal transplant
Hochman (1983)	2	No, yes	No, yes	Indeterminate	(1) Prior seizures
Kaiko <i>et al.</i> (1983)	2	Yes × 2	Yes × 2	Indeterminate	Chronic cancer patients
Goetting and Thirman (1985)	1	Yes	Yes	Likely	
Armstrong and Bersten (1986)	2	No × 2	No × 2	Indeterminate, unlikely	(1) Metastatic colon CA
Mauro <i>et al.</i> (1986)	1	Yes	Yes	Indeterminate	
Deeg and Rajamani (1990)	1	Yes	Yes	Likely	Hereditary coproporphyrria
Pryle <i>et al.</i> (1992)	3	No × 3	No × 3	Indeterminate	Sickle cell crisis patients
Hagmeyer <i>et al.</i> (1993)	3	No × 3	Yes, no, no	Indeterminate	(1) Sickle cell disease, promethazine
Stone <i>et al.</i> (1993)	3	No × 3	No × 3	Indeterminate, unlikely, unlikely	(1) Carbamazepine was stopped
Adair and Gilmore (1994)	1	Yes	Yes	Likely	Acute pancreatitis, s/p transplant
Danziger <i>et al.</i> (1994)	1	Yes	No	Indeterminate	EtOH abuse, pancreatic pseudocyst
Liu <i>et al.</i> (1994)	4	Yes × 4	Yes × 4	Likely	Sickle cell anemia
Rodman and Maxwell (1994)	1	No	Yes	Likely	Sickle cell, cellulitis, promethazine
Marinella (1997)	1	No	Yes	Likely	Alcohol-related pancreatitis
McHugh (1999)	1	No	No	Likely	Mg 0.51 mmol/L
Hassan <i>et al.</i> (2000)	1	No	Yes	Likely	ESRD, gangrene
Knight <i>et al.</i> (2000)	1	Yes	Yes	Indeterminate	Recurrent UTIs
Hubbard and Wolfe (2003)	1	No	No	Likely	UTI, possible pyelonephritis
Beaule <i>et al.</i> (2004)	1	No	No	Indeterminate	
Seifert and Kennedy (2004)	2	No × 2	No × 2	Indeterminate	
Dunwoody <i>et al.</i> (2006)	1	No	No	Likely	Sickle cell anemia/crisis
Gozdemir <i>et al.</i> (2008)	1	Yes	Yes	Indeterminate	
Nagler <i>et al.</i> (2008)	1	No	Yes	Indeterminate	Alzheimer's disease

CA, cancer; EEG, electroencephalogram; ESRD, end-stage renal disease; EtOH, ethanol; UTI, urinary tract infection.

The mean age ($\pm$ standard deviation) of all reported patients suffering a possible seizure (for whom age was available) was 31.8 ± 19.9 years; excluding patients under the age of 18, the mean age was 39.5 ± 15.9 years. The described seizure semiology in 32/50 patients (64%) is that of a generalized convulsion; other presentations include tremulousness, myoclonic jerks, disorientation, hallucinations, and focal seizure. Postictal confusion is described in 9 of the 50 cases (18%). Fifteen cases (30%) had EEG performed; of these, epileptiform abnormalities were seen in 3 EEGs, 6 EEGs were normal, and 6 with generalized slowing. Neuroimaging was obtained in 20/50 patients (40%); of these, two showed atrophy and the others were unremarkable.

Comorbidities were frequent in the cases reviewed. Ten of the 50 reported patients (20%) had renal impairment, and 3/50 patients (6%) had liver impairment. Other confounding conditions included alcohol abuse (Danziger *et al.*, 1994; Marinella, 1997), infection (Rodman and Maxwell, 1994; Knight *et al.*, 2000; Hubbard and Wolfe, 2003; Eker *et al.*, 2009), prior seizure history (Hochman, 1983; Stone *et al.*, 1993), sickle cell disease (Pryle *et al.*, 1992; Hagmeyer *et al.*, 1993; Liu *et al.*, 1994; Rodman and Maxwell, 1994; Nadvi *et al.*, 1999; Dunwoody *et al.*, 2006), and malignancy (Szeto *et al.*, 1977; Kaiko *et al.*, 1983; Armstrong and Bersten, 1986). One patient had Alzheimer's disease (Nagler *et al.*, 2008), one had hereditary coproporphyrria (Deeg and Rajamani, 1990), and one had severe burns and hyponatremia (Kyff and Rice, 1990).

The likelihood of seizure diagnosis being accurate was based on the reported semiology and presence of a typical postictal state. If one of these was atypical, ancillary studies (i.e., EEG) needed to be supportive of the seizure diagnosis to deem this likely. Otherwise, the event was classified as either indeterminate or unlikely seizure. Of the 50 reported patients with meperidine-associated seizures, 20 were deemed likely to be seizures, 26 indeterminate, and 4 unlikely.

Discussion

We discovered a total of 50 cases of meperidine-associated seizures, the majority of which were documented in case report form. These cases were published over the time period of 1967–2012, further emphasizing the relatively low number of published cases, despite previously more widespread use of meperidine compared with today (Hastie *et al.*, 2014). Twelve of the reported seizure cases occurred in pediatric patients of age 18 years or younger. In many of the cases we reviewed, confounding comorbidities were present that may have contributed to seizure occurrence, such as sickle cell disease and malignancy. The presence of these comorbidities further complicates the generalizability of putative toxicity.

The postulated mechanism leading to meperidine-associated seizures relates to the metabolite, normeperidine. Meperidine is normally metabolized by the liver to meperidinic acid and normeperidine (Gutstein and Akil, 2006). Normeperidine is in turn excreted renally. It is this excretion route, which makes renal impairment a possible predisposing factor to meperidine-associated seizures. Furthermore, with oral meperidine administration, higher doses are required for an equianalgesic effect (Gutstein and Akil, 2006). This, however, results in potentially higher metabolite accumulation due to first-pass metabolism.

The epileptogenic effects of normeperidine in humans have been largely explored in a circumstantial manner. Kaiko *et al.* (1983) noted elevated normeperidine levels as well as elevated normeperidine/meperidine ratios in 10 patients with either myoclonus or grand mal seizure; however, only two of these patients were determined to have seizures by those investigators. Szeto *et al.* (1977), Armstrong and Bersten (1986), and Stone *et al.* (1993) also documented that normeperidine levels in adverse reactions related to meperidine administration, although most of the cases they describe are not compelling for seizure activity. Other isolated case reports have been published associating elevated serum normeperidine levels with seizure activity (McHugh, 1999; Hassan *et al.*, 2000; Knight *et al.*, 2000).

However, the relatively low reported number of such cases suggests that despite seizure being a potential adverse effect, it may not be common. In a study of 550 pediatric patients with sickle cell disease [which itself has been shown to predispose to seizure activity (Ali *et al.*, 2010)], the incidence of seizures with meperidine was only 0.4% (Nadvi *et al.*, 1999). Commonly cited predisposing factors to meperidine-associated seizures include impaired renal function, receiving meperidine through patient-controlled analgesia, and high doses of meperidine (Seifert and Kennedy, 2004).

Meperidine dose and route of administration may have contributed to seizure likelihood as well. In our study, high doses in adult cases were considered as >500 mg in 24 hours, medium doses as 100–500 mg in 24 hours, and low doses as <100 mg in 24 hours. In our review, only two patients had reported seizure complications at low doses.

In addition to analgesia, meperidine significantly decreases the temperature threshold for shivering in hypothermic subjects (Kurz *et al.*, 1997). This property has been exploited for use in trials exploring hypothermia as a therapeutic measure (Hemmen *et al.*, 2010) as shivering may prevent subjects from reaching the desired hypothermic target temperature. Other mu-class opiates do not suppress shivering, but the very expensive sedative dexmedetomidine does (Sessler, 2009). Current practice in therapeutic hypothermia calls for meperidine combined with buspirone (Mokhtarani *et al.*, 2001) due to the excessive cost of dexmedetomidine. Our data suggest that the putative toxicity of meperidine is far less than quoted, making meperidine the preferred antishivering agent.

Our study is limited by its nature as a retrospective review of the literature. It is also likely that patients with meperidine-associated seizures in many cases were not reported. Nevertheless, we found that clinical evidence relating meperidine use to seizures is scant overall, emphasizing the weakness of this association. Literature reports of seizures due to meperidine are confounded by use of other medications with potentially epileptogenic potential (Rodman and Maxwell, 1994), malignancy (Szeto *et al.*, 1977; Kaiko *et al.*, 1983; Armstrong and Bersten, 1986), renal impairment (Kaiko *et al.*, 1983; Adair and Gilmore, 1994), prior seizures (Hochman, 1983), and sickling diseases (Pryle *et al.*, 1992; Hagmeyer *et al.*, 1993; Liu *et al.*, 1994; Rodman and Maxwell, 1994; Nadvi *et al.*, 1999; Dunwoody *et al.*, 2006). The cases we reviewed included a significant number of pediatric patients (12/50 patients; age range 15 days to 17 years) in whom the metabolism and elimination of meperidine are lower (Pokela *et al.*, 1992). The exact

difference in normeperidine metabolism between pediatric and adult patient remains unclear.

In summary, the seizure risk with meperidine appears to be significantly overstated. Its judicious use should continue to be explored for conditions in which it has shown efficacy, in particular mitigating shivering in therapeutic hypothermia.

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Authors' Contributions

Dr. Patrick Lyden and Dr. Thomas Hemmen contributed to the study design and conceptualization. Dr. Konrad Schlick performed the literature search, compiled data for analysis, and drafted the initial manuscript. All authors contributed to the writing and revision of the manuscript.

Author Disclosure Statement

No competing financial interests exist.

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