Managing unplanned severe opiate withdrawal after Vivitrol

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Having deliberately precipitated opiate withdrawal with naltrexone (NTX) in several thousand opiate-dependent patients, using a variety of techniques, between 1985 and my retirement two decades later, I think I can comment usefully on the difficulties experienced by Wightman et al. [1] in managing severe and unexpected opioid withdrawal precipitated by Vivitrol®. The drug that is notably absent from their attempts at symptom control is octreotide. Other researchers have confirmed my original observation [2] that it effectively prevents the profuse diarrhea and vomiting that distress medical and nursing staff as well as patients and it is now routine in most rapid NTX induction/transfer programmes [3,4]. 100–200 μg s/c or slow i/v is usually adequate for an average-sized patient. It can be repeated 8-hourly and may need to be continued for several days after initiating NTX; occasionally longer.

Most of my patients transferred seamlessly from opiates to NTX using techniques that did not involve general anaesthesia [5] but mainly after 1995, some 700 were treated in ICUs using a variety of anaesthetic techniques and agents. Dexmedetomidine was not then routinely available in Britain but i/v clonidine very effectively controlled both hypertension and tachycardia and has effective antidotes if BP or pulse-rate drops too far. I should add that the only (relatively minor) anaesthetic complication among those 700+ patients involved an ectopic bronchus, requiring re-intubation after chest x-ray.

In the sort of emergencies described in the paper, clonidine should be given i/v or at least i/m and usually in much larger doses than 100 μg. Many of my patients initiated NTX using an in-patient version of the 24-hour 'Asturian' NTX induction technique, developed originally in northern Spain as a domiciliary procedure without doctors or nurses [6]. It involves premedication with 450 μg of oral clonidine (as well as octreotide, other anti-emetics, gastro-protectants and oral midazolam) and a further 300 μg of clonidine an hour after administering 50 mg of oral NTX. Clonidine is a very safe drug.

The transient but sometimes profound restlessness and delirium that are usual in precipitated withdrawal can be managed by physical restraint but this may need two or three people. In the long-established Perth day-patient NTX induction programme [7] using modest levels of sedation with midazolam, family members or friends provide the muscle-power. In most ICUs, that is probably not acceptable but provided cardiovascular and gastrointestinal disturbances are well-controlled, the choice of anaesthetic is probably not very important. Intramuscular ketamine was sometimes used as an induction agent in patients with no easily accessible veins, allowing venous access to be obtained at leisure, and might be a suitable agent for quickly and safely controlling patients in acute withdrawal. My sole contribution to the anaesthetic literature was a paper describing its use for electro-convulsive treatment [8] in patients in a developing country who were often very psychotic by the time they arrived at the hospital. In subsequent correspondence, we noted that "…the induction of distraught, uncooperative or agitated patients was made considerably easier and less unpleasant for staff and patients" [9].

Antipsychotic drugs like haloperidol have little effect on the delirium of precipitated opiate withdrawal (or *delirium tremens*) and should be avoided. Prevention, by giving a naloxone challenge before Vivitrol, is obviously preferable. However, I also recall a newly-detoxified patient who showed no withdrawal response after successive doses of 400 μg and 800 μg of i/m naloxone but telephoned me 20 min after I then inserted a NTX implant to describe classic but fortunately relatively mild precipitated withdrawal symptoms.

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Dangerous manifestations of reversible cerebral vasoconstriction syndrome

The spectrum of dangerous manifestations of reversible cerebral vasoconstrictive syndrome (RCVS) includes, not only the subtype characterised by rapid-onset headache, as in the recently reported case [1], but also subtypes characterised by potentially life-threatening manifestations such as status epilepticus (SE) [2], and Guillain-Barre syndrome (GBS) [3, 4], respectively.

In one report, ten cases of SE were identified from a clinical database of 77 patients with RCVS (alternatively known as posterior reversible encephalopathy syndrome) in one university center [2]. Their mean age was 38.6 years (range 7 to 73 years). At the time of diagnosis of SE two patients had generalised convulsive SE, and eight had nonconvulsive SE with or only subtle clinical signs such as lip smacking and lateralised automatism, twitching, blinking, and spontaneous nystagmus. During the course of their hospital admission eight patients had generalised tonic-clonic seizures. Six patients responded to first line antiepileptic drugs. Four patients, however, developed refractory SE, and required general anaesthesia to control seizure activity. All ten patients eventually recovered from SE, along with resolution of imaging studies [2].

RCVS can also present with Guillain-Barre syndrome (GBS) [3] or its brainstem variant, Bickerstaff's brainstem encephalitis [4]. Guillain-Barre syndrome was reported in a previously healthy 63 year old woman initially presented with paresthesiae in both feet, and subsequent headache, bilateral visual loss, and hypertension. Magnetic resonance imaging (MRI) studies were consistent with a diagnosis of RCVS. Three days later she developed clinical features of GBS, complicated by respiratory failure requiring mechanical ventilation. Her symptoms improved only after plasmapheresis, and she was eventually weaned off the mechanical ventilation. Brain MRI performed 6 weeks after onset of her symptoms disclosed complete resolution of the abnormalities documented on admission [3]. The authors of the report documented eight other cases of RCVS-related GBS (age range 57–76) in the medical literature. They postulated that the association might be attributable to GBS-related dysautonomia that can lead to life-threatening arterial pressure instability and alteration in brain circulatory self-regulation.

They also postulated a gender-related susceptibility, given the fact that all the cases in their literature review were females [3]. The association of RCVS and Bickerstaff's brain stem encephalitis was reported in a 75 year old woman who presented with headache, new-onset hypertension, and the association of left eyelid ptosis and limitation of extraocular movements in the left eye [4]. Computed tomography angiography ruled out cerebral aneurysm. MRI showed stigmata consistent with RCVS. She subsequently developed right side ptosis and bilateral oculomotor and trochlear nerve palsy, followed by clinical and laboratory stigmata of peripheral demyelinating neuropathy. A subsequent complication was the development of impaired consciousness and euvolemic hyponatremia, the latter attributable to the syndrome of inappropriate antidiuretic hormone secretion. Her conscious level and ophthalmoplegia improved after plasmapheresis. The hyponatremia was also gradually corrected. Two months later she had completely recovered [4]. Conversely, however, reversible cerebral vasoconstriction syndrome can develop as a complication of the use of intravenous immunoglobulin for treatment of Bickerstaff brain stem encephalitis [5]. The latter complication occurred in a 25 year old woman who had been admitted with typical neurological stigmata of brain stem encephalitis, followed by clinical and laboratory stigmata of demyelinating peripheral neuropathy, in association with a cerebrospinal fluid protein content of 80.2 mg/dL. The MRI study performed on admission was normal. Due to rapid progression of her disease she was treated with intravenous immunoglobulin. Forty eight hours after initiation of that treatment she experienced further neurological deterioration, and also subsequently became comatose. A second MRI study showed stigmata of RCVS in the cerebral hemispheres, vertebral artery vasospasm, and brainstem edema. At no stage of her hospital stay did she experience hypertension. She improved markedly after plasmapheresis, and the MRI showed a decrease in the RCVS-associated bihemispheric lesions, with only a small parieto-occipital infarction. By contrast brainstem edema persisted. After 3 months intense rehabilitation she was completely orientated and she could walk, although binocular ptosis, ocular palsy, and dysphagia persisted [5].

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Patient factors associated with nationwide emergency department utilization for cellulitis

1. Introduction

Although studies have estimated costs associated with inpatient admissions for cellulitis, data on emergency department (ED) utilization for cellulitis-related visits are limited [1, 2]. Importantly, the existing literature lacks an analysis of epidemiological factors that may be associated with ED utilization for cellulitis-related visits. In this study, we employ a nationally representative emergency department database to 1) characterize the utilization of ED services for cellulitis-related visits and 2) describe epidemiolocal factors associated with greater likelihood of ED visits for cellulitis.

2. Methods

We conducted a cross-sectional study using the 2013 Healthcare and Cost Utilization Project National Emergency Department Sample (HCUP-NEDS), a national US dataset containing approximately 135 million hospital-based emergency department visits [3]. Patients with a primary International Classification of Diseases, Ninth Revision (ICD-9) code corresponding to cellulitis were included. The validity of these measures for accurately classifying cellulitis has previously been established [4]. Patients with atypical distributions including laryngeal, pharyngeal, or orbital cellulitis were excluded. In addition, patients with a procedure code for incision and drainage of skin and subcutaneous tissue (86.04) were excluded to eliminate cellulitis complicated by abscess. Demographics and clinical characteristics were calculated overall and for visits with a primary diagnosis of cellulitis. Multivariable logistic regression analysis of visit characteristics associated with a primary diagnosis of cellulitis was performed. Survey procedures in SAS 9.4 (SAS Institute) were used to account for the HCUP-NEDS sampling design. This study was deemed exempt by the Partners Healthcare Institutional Review Board.

3. Results

Of 134.9 million ED visits in 2013, 2.9 million (2.1%) were related to cellulitis, resulting in total ED and inpatient service charges of $4.2 billion and $9.5 billion, respectively. Patients evaluated for cellulitis had a mean (SE) age of 39.2 (0.25) and 48.3% were female (Table 1). The lower extremities were most commonly affected anatomic region among patients seen for cellulitis (46.1%). The most common insurances for these patients were Medicaid (27.2%), self-pay (25.3%), and private (23.2%). ED patients seen for cellulitis had lower ED-related healthcare spending ($1696 vs $2699) and a shorter mean length of inpatient hospitalization (4.1 days vs 4.8 days) compared to all other ED patients whose visits were unrelated to cellulitis. Most patients evaluated for cellulitis (84.6%) were discharged home.

A multivariable analysis adjusting for age, gender, payer, day/month of visit, hospital region, location, and median household income suggests that ED patients evaluated for cellulitis were more likely to be of lower socioeconomic status (SES) relative to those with other diagnoses. Medicare, Medicaid, and self-pay patients were more likely to have a cellulitis-related visit compared to patients with private insurance (Table 2). Patients belonging to the lowest quartile by median household income were more likely to have an ED visit for cellulitis compared to patients in the highest quartile (OR 1.15; 95% CI, 1.10–1.21). There was also an inverse association between median household income category and likelihood of cellulitis-related ED visits.

4. Discussion

This study highlights nationally representative healthcare utilization patterns associated with cellulitis-related ED visits, which accounted for