Managing alcohol withdrawal syndromes: the place of guidelines

Alcohol misuse poses a significant problem in terms of morbidity, mortality and cost. Alcohol detoxification and treatment for associated vitamin deficiency syndromes is simple and saves lives. This article discusses the reasons for poor guideline adherence and the current evidence base behind the formulation of these guidelines.

Alcohol misuse, a cause of significant morbidity and mortality, is showing a marked increase in incidence across the UK (Alcohol Concern, 1999), particularly among teenagers (McMiller and Plant, 1996).

In 2006–7, there were 207 788 NHS hospital admissions in England with a diagnosis related to alcohol (NHS Information Centre for Health and Social Care, 2008). This number has more than doubled since 1995–6 (NHS Information Centre for Health and Social Care, 2008). (In children under the age of 16 years, figures related to alcohol admissions have increased by over one-third.) Increasing rates of assessment and admission for alcohol-related syndromes have been seen in the Royal Liverpool University Hospital; between April 2007 and May 2008, 11% of the near-9000 acute medical unit admissions were for the management of alcohol-related syndromes. This has increased by 11% over the last 5 years.

In 2004 the government estimated that alcohol misuse costs the NHS in England between £1.4 and £1.7 billion per year (NHS Information Centre for Health and Social Care, 2008). In 2007, 112 267 prescription items for drugs for the treatment of alcohol dependency were prescribed in primary care settings in England, an increase of 20% since 2003 (NHS Information Centre for Health and Social Care, 2008).

Alcohol misuse is associated with both acute and chronic sequelae. Acute alcohol withdrawal poses a significant risk of withdrawal seizure and delirium tremens, and is associated with up to 20% mortality (Adinoff et al, 1988), falling to only 1% when patients are managed with an appropriate benzodiazepine reducing regimen (Stockwell et al, 1994; Pirmohamed et al, 2000). Chronic misuse is associated with irreversible and significant liver damage, oesophageal carcinoma, peripheral neuropathy and a continuum of CNS defects arising as a result of thiamine deficiency, namely the Wernicke–Korsakoff phenomenon.

Deprivation of thiamine causes damage to mamillary bodies, thalamus, hypothalamus, cerebellar vermis and various cranial nerves, including III, IV, VI and VIII. Its critical role in three enzyme pathways is assumed to cause this damage:

1. Conversion of pyruvate to acetyl co-enzyme A via pyruvate dehydrogenase, a deficiency of which leads to lactic acid excess and ineffective oxidative phosphorylation
2. Converting α-ketoglutarate to succinate within the Krebs cycle, a deficiency of which leads to reduced energy use within the cell. As neurons have greater metabolic demands, a deficit results in cellular death
3. Catalysis by transketolase in the pentose monophosphate shunt, vital for maintainance of the myelin sheath.

The Royal College of Physicians of London issued guidance in 2001 regarding the management of alcohol misuse in the inpatient setting (Royal College of Physicians of London, 2001; Thomson et al, 2002). The main recommendation is the presumptive diagnosis of Wernicke's encephalopathy in all patients exhibiting any signs of chronic alcohol misuse plus any one of the following: confusion, ataxia, reduced Glasgow Coma Score, ophthalmoplegia or hypothermia with hypotension. Patients considered to be at high risk should receive one pair of Pabrinex ampoules (Archimedes Pharma, Reading) once daily for 3 days and those with established Wernicke's encephalopathy at the time of assessment should receive two pairs thrice daily for 3 days minimum. Pabrinex is currently the only UK licensed parenteral vitamin B complex compound.

Previous studies in 2000 revealed that 12% of accident and emergency attendances to the Royal Liverpool University Hospital, which has the largest accident and emergency department in Europe, were alcohol related (Pirmohamed et al, 2000). In parallel with programmes to reduce alcohol burden, appropriate management of inpatients can reduce mortality, morbidity, length of stay, and thus risk of hospital-acquired infection and overall cost. Historically, any guideline adherence has been poor (Caban et al, 1999; Nathwani et al, 2002),

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worldwide, in the UK and within the Royal Liverpool University Hospital (Collini et al, 2007). Before attempting to improve current management mechanisms with education and other intervention strategies, an assessment of current practice, including guideline adherence, was undertaken.

Aims

- To prospectively assess the management of consecutive patients admitted to the regional clinical pharmacology service for alcohol detoxification
- To describe this patient cohort and to describe the adherence to detoxification guidelines, including adherence to vitamin B complex and thiamine prescribing. Furthermore to assess the appropriateness of benzodiazepine prescribing (see below)
- Finally to describe outcome, including length of stay.

Methods

During September 2007, all consecutive consenting patients were enrolled. Their initial management was compared to the Royal Liverpool University Hospital guidance on detoxification. This guidance is based on the Royal College recommendation and Scottish Intercollegiate Guidelines Network guidelines (Thomson et al, 2002; Scottish Intercollegiate Guidelines Network, 2003).

In brief, the guidance comprises management of vitamin deficiency with replacement therapy and detoxification using a chlordiazepoxide reducing regimen. Appropriate assessment for the presence of Wernicke's encephalopathy in any known or suspected alcohol misuser (cardinal signs including confusion, ataxia, ophthalmoplegia and memory problems) is followed by diagnosis as being low risk, high risk or established Wernicke's encephalopathy. As regards treatment, low-risk patients should receive 100 mg thiamine three times daily, high-risk one pair of Pabrinex ampoules once daily for 3 days and those with established Wernicke's encephalopathy should receive two pairs of Pabrinex ampoules three times daily for 3 days.

Results

Over a 1-month period 20 patients were enrolled, of whom 10 were male. The median age in males was 42 years (range 21–61 years) and in females was 50 years (range 24–55 years). The median length of stay was 22 days (range 4–56 days).

When reviewing those with admission over 1 week (6/20) the major reasons were related to social situation, particularly in those with no fixed abode (n=5). Of the 20 patients, only 11 were referred to the specialist alcohol team on hospital admission. Only one (5%) patient had any documented evidence of assessment for the presence of the cardinal signs of Wernicke's encephalopathy (nystagmus, confusion, ophthalmoplegia or ataxia).

Fourteen of 20 (70%) patients were mis-prescribed Pabrinex, the commonest prescribing error being two pairs of ampoules twice daily, constituting underdosing in established Wernicke's and overdosing if considered high risk only. Of concern, it was found that of Pabrinex-eligible patients, only 20% received the recommended dosage of 3 days minimum.

In addition, 70% (14/20) of patients were receiving a sub-therapeutic dose of thiamine; commonly 100 mg twice daily or 300 mg once daily. Furthermore, 50% of patients were prescribed both Pabrinex and thiamine concurrently; while not dangerous this is cost ineffective as there is no proven additional benefit to this.

Of the 20 patients, 10 were referred to the hospital alcohol specialist nursing team during the inpatient stay. Of those 10, 30% (6) had an Severity of Alcohol Dependance Score (alcohol dependance severity) >31 signifying severe dependence; such cases were managed with excessive doses of chlordiazepoxide as required. This is not evidence based and does not follow a reducing regimen and should therefore be avoided.

Discussion

Despite a relatively small sample size, this study contributes to the current literature with regards to both guideline adherence in general and, more specifically, in relation to alcohol detoxification.

Inadequate assessment, poor documentation and subsequent misprescribing were seen in the majority of patients and in all severities of withdrawal syndrome. These findings mirror older North American studies. In the late 1980s, in Boston, only 16% of patients with Wernicke's encephalopathy treated with inappropriately low doses of thiamine (50–100 mg/day) ever made full neurological recoveries (Victor et al, 1989). In 1998, Cook et al found that 85% of inappropriately managed survivors progressed to develop Korsakoff's psychosis, 25% of whom required long-term institutionalization. However, as few current and historic data exist, the current study adds to the available literature. The failure of guideline adherence is not surprising and is ongoing despite dissemination attempts by combining education, audit and feedback. Interestingly, within the British health-care system, systematic review of guideline implementation strategies describes modest to moderate effects with insufficient resources and usually only short-lived effects (Grimshaw et al, 2004). To improve guideline adherence, a multi-faceted approach is required, combining both a persuasive educational programme with formulary restriction and adequate resources, with future re-audit post-implementation.

As to the appropriateness of the current guidance the evidence base remains poor. The most recent Cochrane review (Day et al, 2004) correctly suggests that there is insufficient randomized controlled trial evidence available to guide the physician as to the optimum dose, route, frequency and duration of thiamine treatment required

to prevent Wernicke's encephalopathy. The estimated dose of thiamine required to prevent or treat Wernicke's encephalopathy is believed to be >500 mg once or twice daily, parenterally for 3–5 days (Cook et al, 1998). However, this estimate is based on empirical clinical practice and results from uncontrolled trials.

The first randomized double-blind multidose study into the therapeutic benefits of thiamine in alcohol-dependant patients was conducted by Ambrose et al (2001). This found an intramuscular dose of >200 mg was required to show improvement in this group. Absorption of thiamine is an active, rate-limited process. In a healthy person, the maximum absorbed from a single oral dose is 4.5 mg. Thomson (2000) found that a single oral dose of 30 mg will achieve this level and no increased absorption occurred with any larger single dose. The same study found that alcohol itself reduces thiamine absorption by up to 50% in a third of patients studied. Furthermore, malnutrition in chronic alcohol misusers reduces thiamine absorption by up to 70%. Indeed, multiple studies have shown that parenteral doses of 100 mg daily do not prevent death in all patients and anywhere up to 1 g may be required (Nakada and Knight, 1984; Lindberg and Oyler, 1990; Cook et al, 1998).

The Royal College guidance recommends 100 mg three times daily, providing a total of 13.5 mg/day, sufficient for healthy or mild deficiency states only. Hence the oral route should be restricted to patients not deemed to be at acute risk of deficiency as it is not safe to rely on oral therapy in vulnerable patients.

On the basis of the multiple co-factors affecting thiamine absorption in alcohol misuse and the lack of a standard absorption or utilization test available to assess uptake in patients with established deficiency disease states, the Royal College of Physicians recommends that the confused, ataxic drunk in the accident and emergency or acute medical assessment unit who has evidence of chronic alcohol misuse and has a poor diet and/or no fixed abode should be given intravenous Pabrinex on admission, regardless of whether hospital admission is likely (Royal College of Physicians of London, 2001; Thomson et al, 2002).

The only potential caveat to this approach remains the proposed risk of anaphylaxis associated with parenteral thiamine. Until September 2007, Pabrinex was restricted to patients in whom parenteral treatment was essential. This recommendation followed Commission on Human Medicines guidance published in 1989 based on studies of intramuscular Parentrovite, resulting in 41 cases of anaphylaxis throughout 1970–1988. Pabrinex is associated with a lower incidence of adverse side effects, and Wren and Slovis (1992) studied 15 years of parenteral thiamine prescription, given >10 000 times per year by slow intravenous infusion without any adverse reactions. Hence, intramuscular Parentrovite is no longer licensed for use in favour of the safer, slow infusion intravenous Pabrinex. As a result, the British National Formulary (Joint Formulary Committee, 2009) updated guidance as of September 2007 now states that the risk of anaphylaxis: 'should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke–Korsakoff syndrome where treatment with thiamine is essential.'

The Royal Liverpool University Hospital operates a specialist alcohol dependency nursing team who help patients with the detoxification process. Their role is to determine the alcohol dependency score using the Severity of Alcohol Dependance Questionaire developed by the Addiction Research Unit at Maudsley Hospital (Stockwell et al, 1983). This is used to determine the duration of chlordiazepoxide substitution required and whether or not the patient is suitable for home detoxification. Failure to refer to the team on admission, as occurred in nine (45%) patients, will result in delayed and inaccurate prescribing.

Further studies are urgently required with regards to appropriate management of these patients, but before this adequate guideline adherence is needed.

Conclusions

The increasing burden of alcohol misuse has significant implications for morbidity and mortality and also cost implications, in the immediate setting with regards to length of stay and also long-term outcomes, such as institutionalization for those developing chronic complications. BJHM

KEY POINTS

- Increasing alcohol misuse has led to increasing numbers of admissions for the management of alcohol withdrawal syndromes.
- Royal College guidance is available to assist the clinician in the management of alcohol withdrawal and the prevention of vitamin deficiency.
- Treatment of vitamin deficiency syndromes is simple and cost effective.
- Poor guideline adherence is common and may affect morbidity and mortality outcomes.

Conflict of interest: none.

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