CASE REPORT

Cough, codeine and confusion

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SUMMARY

Codeine is widely prescribed in clinical practice with over the counter (OTC) preparations of codeine freely available for consumption typically as a component of remedies for the common cold/cough. We describe the first reported case of acute confusional state in a previously healthy 14-year-old girl ultimately attributed to inappropriate codeine use. The usage of codeine in the paediatric setting has been highlighted in recent years with many reported deaths—mostly due to respiratory depression. The risks associated with codeine usage may be particularly unnecessary with OTC cough suppressants as evidence of efficacy is absent. Finally, codeine dependence is a common problem among adults and has been reported locally and internationally among adolescents. The combination of lack of efficacy, risk of acute intoxication and dependence, suggests that the use of OTC codeine preparations may be unwarranted.

BACKGROUND

This case provides an invaluable example of the importance in maintaining an open mind in the assessment of patients with acute confusion. In addition to its clinical significance, it explores efficacy, toxicity and dependence on a drug with an overestimated safety profile in the paediatric population. Finally, the recent publication of guidelines from the European Medicines Agency (EMA) regarding codeine usage in paediatrics, provides an interesting backdrop and highlights these new guidelines to unaware readers.

CASE PRESENTATION

A previously well 14-year-old girl presented to the Emergency Department of a General Regional Hospital in Ireland, with a 5-day history of fluctuating confusion and anterograde amnesia. The patient's parents reported that she had been sleeping up to 20 h a day, had a decreased attention span and was suffering from intermittent headaches. The amnesia and confusion fluctuated throughout the day and the symptomatology was unusual. The patient falsely reported completing tasks, for example, she claimed to have showered when it was apparent to her mother that she had not showered. Additionally, she was noted to be switching languages during her homework. The presentation was preceded by 15 days of 'flu-like symptoms, during which time she was absent from school. There were no concerns raised by school, and the patient was otherwise asymptomatic. There was no history of head injury or other significant medical history. The patient denied illicit drug use; she had a history of well-controlled asthma. She was afebrile, there were no abnormalities on general examination and, specifically, there was an entirely normal neurological examination.

A urine toxicology screen was reported positive for codeine (quantity not specified), no other drugs or metabolites were present. Further questioning revealed that the patient had been taking 2–3 spoonsful daily of codeine cough suppressant, oral codeine phosphate, for the 15 days duration of her 'flu-like' illness. This medication is available over the counter (OTC) in Ireland. While the patient had not exceeded the recommended daily dosage of 3–6 spoonsful, she surpassed the maximum recommended duration of usage of 3 days. Each spoonful equates to 15 mg of codeine and thus the patient consumed a total of 450–675 mg over 15 days, instead of the recommended maximum dosage of 270 mg during any given course of treatment.

INVESTIGATIONS

Baseline laboratory investigations included full blood count, C reactive protein, liver function tests, renal profile and electrolytes—all reported normal. MRI of the brain was entirely normal. Genotyping for the CYP2D6 mutation (ultrafast metabolisers) was not sought as symptoms only developed after exceeding the maximum recommended dosage.

DIFFERENTIAL DIAGNOSIS

The causes of acute confusion in the adolescent setting are wide-ranging including infective, metabolic, psychiatric, vascular and malignant, and, as in this case, toxin-induced. The patient's fluctuating and somewhat unusual symptoms initiated a request for a psychiatry review. Despite these initial assumptions, the symptoms were attributable to codeine intoxication. This highlights the necessity of thorough investigations in even the most 'functional' of presentations.

OUTCOME AND FOLLOW-UP

Five days following admission, the symptoms abated; urine codeine was negative at this time point. Clinical review at 2 weeks postdischarge also showed negative urine codeine, and an asymptomatic well child.

DISCUSSION

Paediatric presentations of codeine intoxication often include central nervous system depression, respiratory depression, pruritus and flushing. Confusion is a relatively unusual complaint. Patients with respiratory depression present with noisy breathing, slow breathing, sighing or even signs of cyanosis. On physical examination, findings

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of meiosis, hyporeflexia, hypothermia and bradycardia may be reported, however, in this case, they were absent.

Codeine phosphate is an OTC cough suppressant. It contains 15 mg of codeine/5 mL. The maximum recommended dosage for an adolescent is 90 mg/day (6 spoonsful).[1] The manufacturer suggests that codeine phosphate should be used for dry or painful cough, however, the mild euphoric effect associated with codeine may ease the severity of other symptoms.[1] The evidence for the efficacy of codeine-containing cough suppressants, and many other cough suppressants, is largely absent.[2] Despite the absent evidence base and obvious risk, codeine-containing cough suppressants are favoured by many parents—possibly due to the added analgaesic effect and widespread perception of the 'strength' of codeine. This is in spite of a lack of evidence for efficacy. Additionally, codeine is associated with a complex side effect profile, which includes dizziness, nausea, vomiting, abdominal pain and constipation.

The maximum recommended daily dosage of oral codeine for children over 12 years old is 240 mg, far above that of oral codeine phosphate (90 mg).[1] In light of this dosage disparity, the risks associated with the cough suppressant would appear minimal. However, the availability of codeine phosphate OTC, and the rare polymorphism associated with ultra-rapid metabolisers, means that risks remain. Extension of the period of usage beyond the recommended maximum of 3 days also exacerbates risks—as in this case.

The risks of respiratory depression associated with the use of codeine in the paediatric setting are becoming increasingly clear. In March 2015, the EMA recommended that codeine should not be prescribed to children aged under 12 years.[3] This was in light of the publication of numerous case reports of fatalities involving the usage of codeine in children aged 12 years. A recent review highlighted seven fatalities among 27 cases of codeine intoxication. Significantly, the report highlighted children predisposed to risk—children with renal failure, children undergoing adenotonsillectomy and those with a CYP2D6 gene polymorphism.[4] Although many of these risks appear related to children aged under 12 years, pharmacovigilance should be maintained when prescribing opioids to any paediatric patients. The EMA has recommended that anyone aged <18 years with serious respiratory problems, or those known to be ultra-rapid metabolisers, should avoid all codeine.[3]

Physical complications of prolonged usage of codeine include perforated peptic ulcers, hepatotoxicity and gastrointestinal bleeding. While these complications are relatively unusual, common psychiatric sequelae include impulsivity, depression, compulsive behaviour and anxiety.[5] The burden of codeine dependence among psychiatric in-patients in Ireland may be due to, or a precipitating factor of, psychiatric illness. Prior to the introduction of revised legislation, 33% of psychiatric in-patients reported often using OTC codeine—this figure decreased to 17% following implementation of restrictions to supply.[6]

Although there was no suggestion of addiction in this case, a local newspaper recently reported problems of dependence among adolescents—a common theme in the Irish media in recent years. A study from the USA suggested the rate of codeine dependence may be approximately 4% among adolescents. The likelihood of misuse was shown to be significantly increased in those from lower socioeconomic classes, females, those who reported poor health and those with a history of a depressive episode.[7] Another study in the USA reported the use of codeine cough syrup mixed with alcohol (so called 'Purple drank') among 6.5% of young adults. This study also showed higher abuse among the more vulnerable members of our society, including minority ethnic groups; lesbian, gay, bisexual and transgender individuals; and those from urban areas.[8] These studies are supported by codeine being reported as second only to marijuana in prevalence of abuse among secondary school students in the USA.[9]

In the context of these prevalence data, the physical and psychiatric sequelae of long-term usage may contribute to significant morbidity. Additionally, codeine has been associated with volumetric changes in dopaminergic white matter, which is of particular concern in the developing brain of adolescents.[10] Finally, other cough suppressants such as dextromethorphan have been associated with confusion and even death among adolescents, highlighting the need for a broad discussion on the impact of OTC medication misuse on young people.[11 12]

This evidence of dependence compounds the many problems associated with codeine cough suppressant. It lacks efficacy, may cause acute toxicity and can lead to dependence in both, the paediatric and adult populations.

To the best of the authors' knowledge, this report outlines the first evidence in the literature, of confusion secondary to codeine intoxication. Parents, pharmacists and medical personnel need to remain vigilant to the potential adverse effects of codeine in this vulnerable patient group.

Learning points

- Careful exclusion of organic causes is required even in the presence of unusual symptomatology.
- There is little evidence for the use of oral codeine phosphate for the treatment of cough.
- Codeine prescription is not advised for those aged <12 years.
- Codeine dependence predisposes and is associated with physical and psychiatric illness, highlighting the significant reductions in morbidity and mortality that are achievable with addressing issues of dependence.
- Codeine dependence compounds the many other problems associated with the use of oral codeine phosphate.

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REFERENCES

1 Niesters M, Overdyk F, Smith T, *et al*. Opioid-induced respiratory depression in paediatrics: a review of case reports. *Br J Anaesth* 2013;110:175–82.
2 Smith S, Schroeder K. Over-the-counter medications for acute cough in children and adults in community settings. *Cochrane Database Syst Rev* 2014;11:CD001831.
3 Health Products Information Leaflet. *Patient Information Leaflet—Codinex*. Dublin, 2009.
4 Pharmacovigilance Assessment Committee. *Codeine containing medicinal products for the treatment of cough and/or cold in paediatric patients*. London: The European Medicines Agency, 2015.

5 Wang X, RH H, HL C. The survey on the state of mental health of 224 cases of cough mixture addicts. *Chin J Soc Med* 2011;28:190–2.
6 Agyapong V, Singh K, Savage M, *et al*. Use of codeine-containing medicines by Irish psychiatric inpatients before and after regulatory limitations on their supply. *Ir J Psychol Med* 2013;30:7–12.
7 Ford J. Misuse of over-the-counter cough or cold medications among adolescents: prevalence and correlates in a national sample. *J Adolesc Health* 2009;44:505–7.
8 Agnich L, Stogner J, Miller B, *et al*. Purple drank prevalence and characteristics of misusers of codeine cough syrup mixtures. *Addict Behav* 2013;38:2445–9.
9 Johnson L, O'Malley P, Bachman J, *et al*. *Monitoring the future national survey results on drug use, 1975–2003, vol.1, Secondary School Students [MD]*. Bethesda: National Institute of Drug Abuse, 2004.
10 Hou H, Yin S, Jia S, *et al*. Decreased striatal dopamine transporters in codeine-containing cough syrup abusers. *Drug Alcohol Depend* 2011;118:148–51.
11 Manaboriboon B, Chomchai C. Dextrometorphan abuse in Thai adolescents: a report of two cases and review of literature. *J Med Assoc Thai* 2005;88:242–5.
12 Logan B, Goldfogel G, Hamilton R, *et al*. Five deaths resulting from abuse of dextromethorphan sold over the internet. *J Anal Toxicol* 2009;33:99–103.