CASE REPORT

Cough mixture abuse and rhabdomyolysis

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Cough mixture abuse is an emerging problem among young men in Oriental countries. Its metabolic consequences have been recognised only recently. Such abusers can develop severe folate deficiency, which may be related to peripheral and central nervous system defects. We report three cough mixture abusers with rhabdomyolysis. All suffered from folate deficiencies and also had a history of anti-psychotic drug use. This represents one more life-threatening side-effect from cough mixture abuse.

Introduction

Cough mixture abuse is an increasingly common problem among young men in both developing and developed countries.[1,2] Severe dental caries, somnolence, and accidental injuries are commonly associated. Renal damage and metabolic acidosis have also been reported.[3] We previously described a novel association with cough mixture abuse, namely severe folate deficiency.[4] This in turn leads to neurological and haematological effects. The former can take the form of brain damage[5,6] and fetal neural tube defects.[7] The latter can result in megaloblastic anaemia[8] and possibly leukaemia.[9] Musculoskeletal side-effects were hitherto unrecognised. We report herein three patients with rhabdomyolysis as a possible complication of cough mixture abuse and folate deficiency.

Case reports

With informed consent, case records of 57 consecutive known cough mixture abusers from five outreach centres (male-to-female ratio=46:11; median age, 31 years; age range, 19-49 years) were reviewed as reported.[4] Three patients were found to have a history of rhabdomyolysis, suggesting more-than-a-chance association.

Case 1

A 32-year-old man was admitted for confusion and uncoordinated limb movements. He had a history of schizophrenia, treated with modecate depot 25 mg monthly. He also volunteered to polysubstance abuse that included alcohol, benzodiazepam, ketamine, and cough tablets (30 per day). His complete blood picture showed leukocytosis (haemoglobin [Hb] 154 g/L, white cell count [WCC] 33 x 10^9 /L, platelet count [Plt] 212 x 10^9 /L). Blood biochemistry showed grossly elevated creatinine phosphokinase (CPK) level (58 500 IU/L; reference level, <250 IU/L). Drug toxicology screening was positive for midazolam, ketamine, and dextromethorphan. Further analysis showed low red cell folate level of 125 μg/mL (reference level, >164 μg/mL). He was treated with vigorous hydration and alkaline diuresis. His CPK level normalised after 1 week, with no neurological sequelae.

Case 2

A 29-year-old man was repeatedly admitted with confusion and rigid tone in all limbs. He had a history of schizophrenia and was previously treated with depot haloperidol 75 mg monthly, and oral chlorpromazine 300 mg daily. He suffered from repeated attacks of fever and leukocytosis (Hb 111 g/L, WCC 19 x 10^9 /L, Plt 194 x 10^9 /L) and a grossly elevated CPK (6660 IU/L) was noted on one occasion. He was initially treated as neuroleptic malignant syndrome (NMS) with bromocriptine and antipsychotics were withheld. However, he had three further attacks over the following year. Urine toxicology screening revealed ephedrine, codeine and dextromethorphan, and he volunteered habitual abuse of cough mixtures (2 bottles/daily). An electroencephalogram showed slow waves, while brain magnetic resonance imaging showed no abnormality. Blood analysis showed a low red cell folate level (63 μg/mL). He was treated with folate supplements and did not suffer any further attacks.

Case 3

A 31-year-old man on sulpiride for delusional disorder admitted to cough mixture abuse (3 bottles daily x 5 years). He complained of myalgia and proximal muscle weakness and swelling.

Key words
Antitussive agents; Cough/drug therapy; Folic acid deficiency; Rhabdomyolysis; Substance-related disorders

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Complete blood picture was normal (Hb 108 g/L, WCC 8 x 10^9 /L, Plt 298 x 10^9 /L) but the CPK level was high (3200 IU/L). There was also renal impairment (creatinine 225 mmol/L) and myoglobinuria. An electromyogram showed a myopathic process with decreased sensory response. An open muscle biopsy showed necrotising myopathy with degenerating fibres and sarcoplasmic vacuolation, while a sural nerve biopsy showed severe axonal degeneration. Urine toxicology screening revealed ephedrine, phenothiazine and dextromethorphan. Incidentally he had macrocytosis (mean corpuscular volume, 110 fL; reference range, 81-90 fL) and his red cell folate levels were low (61 µg/mL). He improved after hydration and vitamin supplements, but was lost to hospital and out-reach clinic follow-up.

濫用咳藥水與橫紋肌溶解症

亞洲地區的男性青少年濫用咳藥水的問題日益嚴重，濫用咳藥水會引致身體機能問題。咳藥水可能導致濫藥者出現嚴重葉酸缺乏，這會破壞中樞及周邊神經系統。本文報告三名咳藥水濫用者出現橫紋肌溶解症的病例。他們均出現嚴重葉酸缺乏，並有服食精神病藥物。這些病例凸顯濫用咳藥水的又一個致命副作用。

Discussion

Cough mixture abuse is often perceived by the public and clinicians as a relatively less harmful substance abuse disorder. However, its metabolic and neuropsychiatric damaging consequences are increasingly recognised.[10] Such abusers are often poly-drug abusers and may suffer from underlying primary or secondary psychiatric disorders. Hence, it is often difficult, and sometimes impossible, to attribute the detrimental effect to cough mixture abuse alone. However, carefully controlled studies demonstrating a dose-effect relationship makes the association between cough mixture abuse and severe folate deficiency appear plausible.[4]

Rhabdomyolysis is an uncommon clinical emergency. It may result in renal shut down, hyperkalaemia, hyperphosphataemia, and death. In one review, drug overdose, alcohol and illicit drug use accounted for 46% of cases.[11] The commonest culprit drugs are stimulants such as cocaine and amphetamine. It can also ensue after prolonged coma due to overdosing with central nervous system depressants. In our cases, the initial differential diagnoses were prolonged stupor, NMS and sepsis, but the diagnosis of cough mixture–related muscle damage was entertained. There was no response to empirical treatment for sepsis or NMS, and toxicology screening did not show the presence of stimulants. Indeed, the clinical features were atypical for stimulant overdoses or NMS. Two patients showed relapsing and insidious clinical courses, indicating a continuous ongoing problem. Finally, all patients were found to have folate deficiency, a hallmark of cough mixture abuse and a known cause of muscle damage, though myoglobinuria was documented in the record of only two of our three cases. Large doses of codeine are known to have myopathic effects.[12] Low folate levels are also reported in myopathic disorders.[13] Rhabdomyolysis also occurs with inborn errors of folate metabolism.[14] All these are suggestive of a causative effect. Interactions with other components (eg pseudoephedrine) impurities or additives in the illicit cough mixture might also aggravate the musculoskeletal damage.[15] For the general public, the possibility of life-threatening rhabdomyolysis represents a further deterrent to cough mixture abuse. For clinicians, a high index of suspicion is needed to facilitate early investigation and treatment, so as to prevent or minimise permanent kidney or muscle damage.

References

1. Desai S, Aldea D, Daneels E, Soliman M, Braksmajer AS, Kopes-Kerr CP. Chronic addiction to dextromethorphan cough syrup: a case report. J Am Board Fam Med 2006;19:320-3.
2. Mattoo SK, Basu D, Balaji M, Sharma A, Malhotra A. Subtypes of codeine cough syrup abusers. Indian J Med Sci 1999;53:97-102.
3. Wong KM, Chak WL, Cheung CY, et al. Hypokalemic metabolic acidosis attributed to cough mixture abuse. Am J Kidney Dis 2001;38:390-4.
4. Au WY, Tsang SK, Cheung BK, Siu TS, Ma ES, Tam S. Cough mixture abuse as a novel cause of folate deficiency: a prospective, community-based, controlled study. Haematologica 2007;92:562-3.
5. Au WY, Cheng TS, Siu TS, Tam S. Cerebellar degeneration and folate deficiency due to cough mixture abuse. Haematologica 2005;90 Suppl:ECR28.
6. 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.
7. Tsang SK, Au WY. Cough mixture abuse in pregnancy, folate deficiency, and neural tube defects? Am J Hematol 2005;78:163.
8. Au WY, Tsang J, Cheng TS, et al. Cough mixture abuse as a novel cause of megaloblastic anaemia and peripheral neuropathy. Br J Haematol 2003;123:956-8.
9. Au WY, Harod KK, Law MF. Cough mixture abuse, folate deficiency and acute lymphoblastic leukemia. Leuk Res 2009;33:508-9.
10. FDA warns against abuse of dextromethorphan (DXM). FDA Talk paper. 2005 May 20. FDA website: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.html. Accessed 19 Oct 2011.
11. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore) 2005;84:377-85.
12. Pokorny CS, Saunders JB. Codeine induced rhabdomyolysis. Aust N Z J Med 1994;24:582.
13. Allen RJ, DiMauro S, Coulter DL, Papadimitriou A, Rothenberg SP. Kearns-Sayre syndrome with reduced plasma and cerebrospinal fluid folate. Ann Neurol 1983;13:679-82.
14. Shoji Y, Takahashi T, Sato W, Takada G. Acute life-threatening event with rhabdomyolysis after starting on high-dose pyridoxine therapy in an infant with homocystinuria. J Inherit Metab Dis 1998;21:439-40.
15. Suzuki T, Masukawa Y, Misawa M. Drug interactions in the reinforcing effects of over-the-counter cough syrups. Psychopharmacology (Berl) 1990;102:438-42.