Cough mixture abuse as a novel cause of folate deficiency: a prospective, community-based, controlled study

Cough mixture abuse has been reported to cause severe folate deficiency and neurological defects. We carried out a prospective case-controlled survey to confirm this association and define the incidence and severity of the problem. A total of 57 cough mixture abusers and 47 other substance abusers (controls) were studied. When compared with controls, cough mixture abusers had a high incidence of low folate levels that could only be detected by screening.

Haematologica 2007; 92: 562-563

Cough mixture abuse accounts for 3% of all registered substances abusers in Hong Kong (HK).[1] The harmful effects of cough mixture abuse include somnolence, dental caries, lactate acidosis[2] and psychosis.[3] We have reported profound folate deficiency with high homocysteine (HC) levels, causing peripheral neuropathy and megaloblastic anemia in cough mixture abusers.[4] Damage may also be seen in the central nervous system[5] and the fetal neural tube.[6] Community screening among cough mixture abusers is needed.

With informed consent, 57 cough mixture abusers (>60 mL daily × 2 months; 46 men, 11 women; median age 32.1) and 47 other substance abusers (controls, 28 men, 19 women; median age 31) were interviewed from five out-reach clinics. There were more men among the cough mixture abusers (p=0.021) but other social features (employment, living conditions, marriage) were matched between the two groups. Blood samples were frozen and batch assayed for total HC and plasma methylmalonic acid (MMA) levels. Normal reference ranges were derived from 20 samples from volunteers stored and processed in parallel. The study was approved by the institution review board.

Among the cough mixture abusers, 16 were poly-substance abusers (benzodiazepam=12, heroin=3, ice/alcohol/cannabis/ecstasy=1 each, undeclared=2). The content of cough mixture is regulated in Hong Kong (*www.psdh.gov.hk/eps/webpage.jsp*) and both codeine (n=33) and dextromethophan (n=18) were abused. Some subjects reported combined usage of the two types (n=5) and use of codeine *pills* (n=1). The median daily volume of cough mixture consumed was 290 ml (range 50-1500 mL). The controls abused a variety of subtances (heroin=22, benzodiazepam=7, alcohol=9, ketamine =7, cannabis=6, ecstasy=5, ice=4, volatile solvent =1, others =2) and 15 of them were polysubstance abusers.

Cough mixture abusers had lower red cell folate (557 vs 786 nmol/L, p<0.001) and serum vitamin B12 levels (193 vs 282 pmol/L, p<0.001) than controls. They also had higher platelet counts (279 vs 230x10^9/L, p=0.015) but comparable hemoglobin concentration (14.3 vs 13.7 g/dL, p=0.07) and mean cell volume (90.0 vs 90.2 fL, p=0.42). The incidence of folate and vitamin B12 deficiencies among cough mixture abusers was 39% (control 6.3%, p<0.001, RR=6.0) and 21% (control 0%), respectively. There was a strong correlation between folate and vitamin B12 levels (p=0.004, R=0.28) and eight patients had concomitant deficiencies in both. The folate-deficient cases consumed a greater volume of cough mixture (481 mL vs. 188 mL, p=0.006).

Table 1. Metabolite and hematologic parameters in folate and vitamin B12 deficient patients.

	HC (μmol/L)	MMA (μmol/L)	B12 low vs. normal	Hb (g/dL)	WCC (×10^9/L)	Platelets (×10^9/L)	MCV (fL)
Low red cell folate (n=25) vs. normal	27.0 vs. 20.3 p=0.002	0.57 vs. 0.25 p=0.30	8/25 vs. 4/79 p<0.001 RR=6.3 (2-19)	14.1 vs. 14.0 p=0.32	5.4 vs. 7.2 p=0.006	257 vs. 255 p=0.94	92.9 vs. 89.3 p=0.028
Low vitamin B12 (n=12) vs. normal	22.6 vs. 21.7 p=0.75	0.33 vs. 0.34 p=0.89	NA	14.3 vs. 14.0 p=0.58	5.5 vs. 6.9 p=0.07	280 vs. 252 p=0.10	88.9 vs. 90.4 p=0.82
Low serum folate (n=10) vs. normal	34.0 vs. 20.6 p=0.026	0.26 vs. 0.35 p=0.75	2/12 vs. 8/92 p=0.33	13.7 vs. 14.1 p=0.54	6.7 vs. 6.7 p=0.99	283 vs. 252 p=0.28	92.1 vs. 89.9 p=0.49

vs. versus; CI: confidence interval; RR: relative risk; NA: not applicable; Hb: hemoglobin (normal 13.0-16.8 g/dL); MCV: mean cell volume (normal 82.0-96.9 fL); WCC: white cell count (normal 4.4-10.1×10^9/L); platelet count (normal 170-380×10^9/L); HC: homocysteine level (normal <50 μmol/L), MMA: methylmalonic acid (normal <0.38 μmol/L) Values are median values and comparisons were made using two tailed Fischer's exact and Mann Whitney U tests.

Although codeine and dextromethophan are both opiates, folate (p=0.004) and vitamin B12 (p=0.004) levels were lower, and platelet counts higher (p=0.003) among cough mixture abusers than among heroin abusers. These values showed no difference between codeine and dextromemorphan abusers. An analysis of metabolites showed no statistically significant differences between cough mixture abusers and controls with regards to HC (21.1 vs 22.5 umol/L, p=0.18) and MMA levels (0.41 vs 0.27 μmol/L, p=0.46). However, when patients with low Fo and B12 were compared against the rest of cohort, folate-deficient patients had higher HC levels. On the other hand, MMA levels were not increased in folate or vitamin *B12*-deficient cases (Table 1).

Macrocytosis (MCV>96 fL) was a poor marker of folate deficiency. Among 18 macrocytic patients (range 96.2-109.8 fL), only 9/18 were cough mixture abusers, and 7/18 had low folate levels. The cough mixture abusers reported psychosis (n=25), numbness (n=23), weakness (n=11), dizziness (n=6) and dental carries (n=49). Patients reporting numbness consumed more cough mixture (470 mL vs. 202 m, p=0.004) and had lower vitamin B12 level (223 vs. 228 pmol/L, p=0.039), while those with psychosis had lower vitamin B12 levels (227 vs. 285 pmol/L, p=0.031), higher HC (24.1 vs. 18.4 μmol/L, p=0.03) and higher consumption of cough mixture (419 mL vs. 223 mL, p=0.04). There was no symptomatic association with folate findings.

Our prospective data showed that cough mixture abuse is associated with low folate levels. This is unrelated to concomitant drug use or the type of cough suppressant (dextromethophan or codeine) abused, and may be dose-dependent. The low folate levels were also unrelated to sugar consumption (absent in codeine pills).[7] Many patients also had low vitamin B12 levels, usually accompanied by low folate levels. Metabolite assays in our published hospital-based study had shown that this is sec-

ondary to severe folate deficiency.[4] Similarly, in this community-based cohort, patients with *low vitamin B12* levels had significantly raised levels of HC (characteristic of folate pathway blockade) but not significantly raised MMA. Finally, we found a novel but unexplained thrombocytosis in cough mixture abusers.

Due to voluntary participation, our study cases may not be representative of all cough mixture abusers.[8] We also failed to identify dietary, genetic and life-style risks for folate deficiency present in 6% of the controls.[9] However, our prospective, community-based study showed that clinical symptoms and hematologic parameters are a poor guide to folate deficiency in at-risk populations. Hence, prospective screening and vitamin supplementation may be needed.[10]

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Funding: this study was supported by the Beat Drugs Fund of the Action Committee Against Narcotics of the Government of the Hong Kong Special Administrative Region.

Key words: cough mixture, folate deficiency, homocysteine.

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ERRATA CORRIGE

In an article published during 2004, an author name was erroneously written (V. LeCam-Duchez, instead of V. Le Cam-Duchez); correct citation becomes:

Giansily-Blaizot M, Verdier R, Biron-Adreani C, Schved JF, Bertrand MA, Borg JY, Le Cam-Duchez V, Briquel ME, Chambost H, Pouymayou K, Dutrillaux F, Favier R, Martin-Toutain I, Verdy E, Gay V, Goudemand J, Navarro R, Durin A, d'Oiron R, Lambert T, Pernod G, Barrot C, Peynet J, Bastenaire B, Sie P, Stieltjes N, Torchet MF, de Moerloose P. Analysis of biological phenotypes from 42 patients with inherited factor VII deficiency: can biological tests predict the bleeding risk? Haematologica 2004;89:704-9.