

Short communication: Malaria and amphetamine 'horse tablets' in Thailand

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Summary

During recent clinical malaria research in Thailand we found a high frequency of amphetamine misuse and withdrawal amongst patients admitted to hospital with *Plasmodium falciparum* malaria. This comorbidity may cause diagnostic confusion, alter malaria pathophysiology and lead to drug interactions.

keywords *Plasmodium falciparum*, malaria, amphetamine, methamphetamine, drug misuse, diagnosis, Thailand, Burma

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Amphetamine and methamphetamine misuse is a severe and increasing public health problem in east Asia (Ahmad 2002). In Thailand an estimated 600 million tablets are used per year (Anonymous 2000). These drugs originate mainly from adjacent Myanmar (Burma) and their Thai names are *yaa ba* or 'mad tablet' and *yaa ma* or 'horse tablet' – so called after the horse emblem on the original amphetamine product (Wellcome Foundation). They are taken, usually by young adult males, for their stimulant effects, to combat fatigue and allow drivers, and farm and factory workers to work for longer hours. In a survey of 57 randomly selected Thai truck drivers, 87% tested positive for amphetamine or methamphetamines in their urine (Mongkolsirichaikul *et al.* 1988). *Plasmodium falciparum* malaria is also a common clinical problem on the Thai/Myanmar border. We noticed a potential interaction between malaria and amphetamine use and investigated this further.

Between May–July 1999 and May–July 2000 we entered 113 Thai and Burmese patients with *P. falciparum* malaria into prospective clinical studies at Mae Sot Hospital, Tak Province, western Thailand (Newton *et al.* 2001). Fourteen patients (12%, 12 with severe and two with uncomplicated malaria) gave a history of recent methamphetamine use, seven in 1999 and seven in 2000. Thirteen of the 14 patients were male; the median age was 26 years (range: 15–48). Two patients became severely agitated, four

developed an unusual affect with anxiety, epigastric or chest pain and nausea, two had urinary retention and one developed hypersomnia (Braitberg & Kunkel 1996; Robson 1999). Three patients had seizures after anti-malarial treatment. One patient with severe malaria was a chronic user of methamphetamines and was biochemically and clinically hyperthyroid, probably secondary to methamphetamine use (Morley *et al.* 1980).

In 2000, as part of clinical studies approved by the Ethical and Scientific Review Committee of the Royal Government of Thailand, we tested urine samples from 29 previously untreated patients who consented and were able to give a urine specimen on the day of admission for amphetamines or methamphetamines and derivatives. We used immunochromatographic dipsticks (Frontline[®] Amphetamines Urine Testing Strips; Roche Diagnostics, Lewes, UK) (Beck *et al.* 2000) with a lower limit of detection of 300 ng/ml. Sixteen of 29 patients (55%) tested gave positive results. None had taken drugs known to give false positive results. Of the seven patients admitted in 2000 who volunteered a recent history of amphetamine use, five were positive and two negative on urine testing. Amphetamine or methamphetamine was also detected, by gas chromatography–mass spectroscopy in the admission urine sample of one patient, but the lower limit of detection was 500 ng/ml, higher than that of the dipsticks.

Urine tests may not detect recent clinically relevant ingestion as the patients are unlikely to have taken amphetamines after becoming unwell, but could be withdrawing [the patients in this series had been unwell for a median of 3.5 days (range: 2–14)]. In addition, the half-life of amphetamines is shortened at acidic urine pH (approximately 8 h) (Beckett *et al.* 1965) and the patients in this series had a median admission urine pH of 5 (range: 5–8), as determined with Combur10 (Boehringer, Mannheim, Germany).

We found a high frequency of recent amphetamine use, from the clinical history and from urine testing, amongst patients admitted to hospitals with malaria. This comorbidity may cause diagnostic confusion, alter malaria pathophysiology, and lead to drug interactions. Malaria has been associated with the injection of illicit opioids via shared needles (Brown & Khoa 1975; Chau *et al.* 2002).

Oral amphetamine misuse by patients presenting with malaria is potentially important for several reasons. First, infectious diseases may be confused with illness caused by substance abuse, with, for example, acute bacterial meningitis misdiagnosed as acute intoxication with hallucinogenic leaves (Baldwin *et al.* 1993). Similarly, severe malaria may be misdiagnosed as amphetamine toxicity and *vice versa* as coma and fever are also features of amphetamine poisoning.

Secondly, acute amphetamine intake, and the subsequent 'crash phase' occurring 2–3 days after cessation, can cause a wide range of symptoms and syndromes, such as hypertension, agitation, abdominal pain, delirium, cardiac dysrhythmias, hyperpyrexia, urinary retention, seizures, hypersomnia, asomnia and hypoglycaemia (Braitberg & Kunkel 1996; Robson 1999), which may cause clinical confusion in caring for a patient with malaria, particularly if he or she is severely ill. If taken by a patient developing cerebral malaria, the amphetamine-mediated central nervous system release of noradrenaline, dopamine and serotonin may alter the pathophysiology and clinical picture. Amphetamine withdrawal can lead to excessive sleepiness prompting concerns that the patient is developing cerebral involvement or hypoglycaemia.

Thirdly, amphetamines interact with other drugs used in the adjunctive treatment of severe malaria such as catecholamines. Mefloquine, an important component of current antimalarial treatment in SE Asia, and amphetamines both have neuropsychiatric adverse effects. Whether they potentiate each other is unknown, but in the absence of this information we avoid prescribing mefloquine in patients known to have taken amphetamines recently.

Fourthly, severely agitated patients may harm themselves and health staff. With the widespread and increasing use of

amphetamines in malarious areas of SE Asia, their use should be borne in mind when treating adults with malaria. More research is required to define the interaction between amphetamine use and malaria.

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