Ingestion of High-Dose Buprenorphine by a 4 Year-Old Child

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To the Editor:

Buprenorphine is a semi-synthetic opioid acting as a partial antagonist of morphine receptors with longer activity than morphine. The main pharmacokinetic characteristics of high-dose buprenorphine are: low therapeutic blood concentrations by the sublingual route owing to a high volume of distribution; extensive metabolism to norbuprenorphine (weakly active), buprenorphine-glucuronide and norbuprenorphine-glucuronide (1); and poor bioavailability by the digestive route, owing to a strong intestinal first-pass effect. Low-dose buprenorphine has been used for about twenty years in the treatment of moderate-to-severe pain. Under the trade name Subutex® II, high-dose buprenorphine (HDB) as sublingual tablets has been approved in France since 1996 for the treatment of opioid dependence. The very large number of patients currently treated with HDB (>70,000) and the parallel increase in abuse practices (i.e. intravenous injection, association with benzodiaze-
pines) resulted in numerous fatalities in which buprenorphine was supposedly involved (2–4). In the US, buprenorphine is the only narcotic treatment option that can be prescribed outside an opiate addiction clinic in a physician’s office after they have taken a special approved 8 hour training course. We report here an unusual intoxication case concerning an opiate naive, 4 year-old child.

Half of a 8 mg Subutex® tablet (part of the father’s treatment) was swallowed by a 4 year-old girl (14.5 kg) at 14:45. Her mother was in the room and took her immediately to the hospital. On admission at the Hospital Pediatric Department (15:00), she was slightly restless. The Glasgow score was at 15, blood pressure at 113/53 and bilateral miosis was noted. After oral administration of activated charcoal (1 g/kg), blood and a urine samples were collected at 18:45 and sent to the laboratory of toxicology. The clinical evolution was favourable as neither cardiac nor respiratory trouble was observed during the following

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993
24 hours. Miosis disappeared the morning after admittance and the girl was discharged from hospital in the evening. Buprenorphine and norbuprenorphine were determined in serum and urine using a previously published liquid chromatography—electrospray—mass spectrometry method (5). Buprenorphine and norbuprenorphine concentrations were respectively 0.64 and 7.7 μg/L in serum, and 173 and 419 μg/L in urine.

Though opiate replacement therapy concerns adults, pediatric poisoning with high-dose buprenorphine is not infrequent, at least in France (6). Buprenorphine exhibits a relatively high therapeutic index. No clinically relevant respiratory effects were observed in volunteers receiving up to 16 mg/day buprenorphine for 84 days in one of the first opioid replacement research protocol (7). This confirmed the relative safety of buprenorphine reported in the 1980’s in overdose cases with low dosage formulations. Furthermore, during clinical safety studies of HDB, respiratory rate and oxygen saturation were found to be minimally affected following sublingual administration of 8 mg buprenorphine to nondependent healthy individuals (8). This limited toxicity can certainly be explained by the partial agonist action of buprenorphine and its reduced oral bioavailability (1). The recently reported fatalities appeared to be in most cases linked to HDB misuse, especially intravenous administration, and its association with other CNS depressants (benzodiazepines and anti-psychotics) (3,4). Since this drug does have the potential to be abused, there is a formulation available in the US that combines buprenorphine with naloxone in a 4:1 ratio respectively. The addition of naloxone, an opioid antagonist, may deter misuse of the drug and abuse by injection. When the combination drug (Subuxone®) is crushed and injected, the naloxone has greater bioavailability than the buprenorphine and withdrawal symptoms will occur. However, when taken sublingually, as prescribed, buprenorphine has a greater bioavailability and the opioid agonist effect used to treat the addiction will prevail (9). The present pediatric intoxication case confirms the relative clinical safety of buprenorphine, as the only symptom observed was bilateral myosis which directly results from the agonist effect of buprenorphine on μ receptors (1).

Buprenorphine exhibits large inter-individual variability of serum concentrations for a same administered dose. Hence, after sublingual administration of a 8 mg tablet to 14 volunteers, the time to maximal concentration (Tmax) ranged from 1 to 4 hours and the peak serum concentration (Cmax) from 1 to 5 μg/L (10). In the present case, activated charcoal may have limited buprenorphine absorption and its bioavailability been decreased owing to the strong intestinal first-pass effect following ingestion of the sublingual form. Of note, the serum concentrations of buprenorphine measured 4 hours after HDB intake are lower than the 24-hour (trough) concentrations observed in adults chronically administered a similar weight-adjusted dosage (0.3 mg/kg). Usually, serum and urine norbuprenorphine concentrations are in the same range as those of buprenorphine (1). In this ingestion case, the norbuprenorphine concentrations are higher than those of buprenorphine in the two biological samples. This confirms an increased buprenorphine metabolism due to an extensive intestinal first-pass effect.

In conclusion, the clinical consequences of an accidental ingestion of buprenorphine by a 4-year-old child were mild.

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