A US-France collaboration to document a drug-facilitated crime using tetrahydrozoline (Visine®)

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Introduction

Topical imidazolines are found in many over-the-counter (OTC) eye and nose decongestants. These drugs have central and peripheral alpha-2 agonist activity. Significant clinical consequences (respiratory depression, hypotension and bradycardia) can occur from ingestions in young children, requiring intensive care management (1). In addition, imidazolines have been used in drug-facilitated sexual assault (2-5) to induce comatose victims that are unable to fend off the perpetrator, with an effect similar to that of clonidine. Products with imidazoline components are numerous and include tetrahydrozoline, sold as Visine®. The medication relieves itching, burning and watery eyes due to pollen and dust (Figure 1). This drug is not available in France.

Case report

A 6-year old boy was living in France with his mother, an American lady, recently divorced. She was unable to take care of him due to low interest. Drowsiness, ataxia, sedation, muscular weakness and marked somnolence were noted at school and during the weekend, when the boy was with his father. These symptoms were present at least for 2 months. The father refused a hair specimen to be collected but asked us to achieve a general unknown screening procedure in urine for sedative drugs. The urine was collected about 18 to 20 hours after the child was no longer in contact with the mother. Routine testing, by LC-MS/MS came back negative. The possibility of using a product not marketed in France, and therefore not screened by the target LC-MS/MS method was an issue. After discussion with an American colleague, a literature search about specific US drugs used in drug-facilitated crimes and the discovery of a Visine® container in the bag of the mother, evidence for potential exposure to tetrahydrozoline exposure was discussed. Therefore, the urine was tested a second time for this specific drug.

Analytical procedure

After internal standard addition (15 ng of glafenine) to 100 µL of urine, 20 mg of a home made QuEChERS salts mixture (6) was added to the sample: $MgSO_4$/NaCl/$C_6H_5Na_3O_7.2H_2O$/$C_6H_6Na_2O_7.1,5H2O$ (4/1/1/0.5; m/m/m/m). After addition of acetonitrile (500 µL), 1 min of vigorous shaking and centrifugation (10,000 rpm for 10 min), the organic phase was collected and subsequently evaporated to dryness at 30 °C under a gentle stream of nitrogen. The dry residue was reconstituted with 70 µL of acetonitrile; 5 µL were injected into the LC-ES-MS/MS system. The calibration curve was constructed in the 1 to 500 µg/L range using ad hoc tetrahydrozoline (Sigma Aldrich, France) additions to drug free human urine.

The chromatographic system consisted of a LC20-ADXR pumping and auto-sampler system (Shimadzu, France), and the separation was performed on an Uptisphere-3SI (100×2 mm, 3 µm i.d.) column (Interchim, France). The mobile phase consisted of (A) a pH 3.0 formiate buffer 2 mM, and (B) acetonitrile with 10 % of A. A flow rate of 0.3 mL/min was used. Separation started with 95 % B for 0.2 minutes, then B decreased to 10 % for 4 minutes maintained for 1 minute; finally, initial conditions were achieved within 0.5 minute and maintained for 2 minutes before the next injection. The total chromatographic run time was 7.5 minutes.

Detection was performed using an API 3200 Qtrap mass-spectrometer equipped with a Turbo-ionspray interface (Applied Bioystems/Sciex, France). Ionization and detection parameters were optimized using the auto-tune function of the MS software by infusion of a 10 mg/L solution of tetrahydrozoline. Ionization in the positve mode (+5.5 kV ionisation voltage) was produced by a turboionspray source heated at 500 °C, using nitrogen as curtain and nebuliser gas. Curtain gas was set at 20 arbitrary units (a.u.), ion source gas 1 and 2 were set respectively at 40 a.u. and 50 a.u. Detection was performed in the selected reaction monitoring (MRM) mode, using the protonated [M+H]+ tetrahydrozoline and glafenine as precursors ions (m/z 201 and 373, respectively); the transitions monitored were m/z 201 →131 for quantitation, m/z 201→91 for confirmation of tetrahydrozoline, m/z 373→281 for glafenine.

Results

Although most authors (2-5) have used GC/MS to test for tetrahydrozoline, we have done it by LC-MS/MS. The LOD and LOQ were 0.5 and 1 µg/L, respectively. The method was linear (1/x weighting) up to 500 µg/L.

The urine of the boy tested positive at 257 ng/mL, demonstrating exposure to tetrahydrozoline within the hours before collection (Figure 2).

Discussion

Visine® contains 0.05 % tetrahydrozoline (500 µg/mL). There is little data in the literature about urine concentrations in children. After administration of 2 drops directly into the conjunctival sac of each eye, 10 adult patients had detectable urine concentrations 24 hours post dosing in the range of 13 to 210 ng/mL (7). In 2 unintentional overdoses, urine concentrations were 49.5 and 9.2 µg/mL, approximately 7 h and 45 min after ingestion, respectively (5). Stillwell and Saady (2) found 1481 ng/mL (7 h after ingestion) and 108 ng/mL (23 h after ingestion) in 2 cases of chemical submission. Finally, Spiller and Siewert (3) detected tetrahydrozoline at 114 ng/mL (20 h after exposure) and about 150 ng/mL in 2 cases of sexual assault.

The measured concentration in the present case is therefore consistent with exposure to the drug for its sedative properties. For that, the drug belongs to a long group of drugs that have been used to obtain lethargy, irrespective of the final purpose (sexual assault, robbery, children or elderly chemically assaulted).

Conclusion

The use of a drug to modify a person's behavior for criminal gain is not a recent phenomenon. However, the sudden increase in reports of drug-facilitated crimes has caused alarm in the general public. Drugs involved can be pharmaceuticals, such as benzodiazepines, hypnotics, sedatives (neuroleptics, some histamine H1-antagonists), anesthetics (GHB, ketamine), drugs of abuse, or more often ethanol. Most of these substances possess amnesic properties and therefore the victims are less able to accurately recall the circumstances under which the offence occurred. As they are generally short-acting, they impair an individual rapidly. Due to their low dosage, a surreptitious administration into beverages such as coffee, soft drinks (cola) or even better alcoholic cocktails is relatively simple.

Tetrahydrozoline is also an ideal drug for drug facilitated sexual assault as it is clear, odourless, readily available, and inexpensive. It can easily be overlooked at crime scene investigation since it is so widely used by the general public and commonly found in homes. Not testing for this compound becomes the perfect poison in France, however international collaboration is of paramount importance, as perpetrators do not have borders.

References

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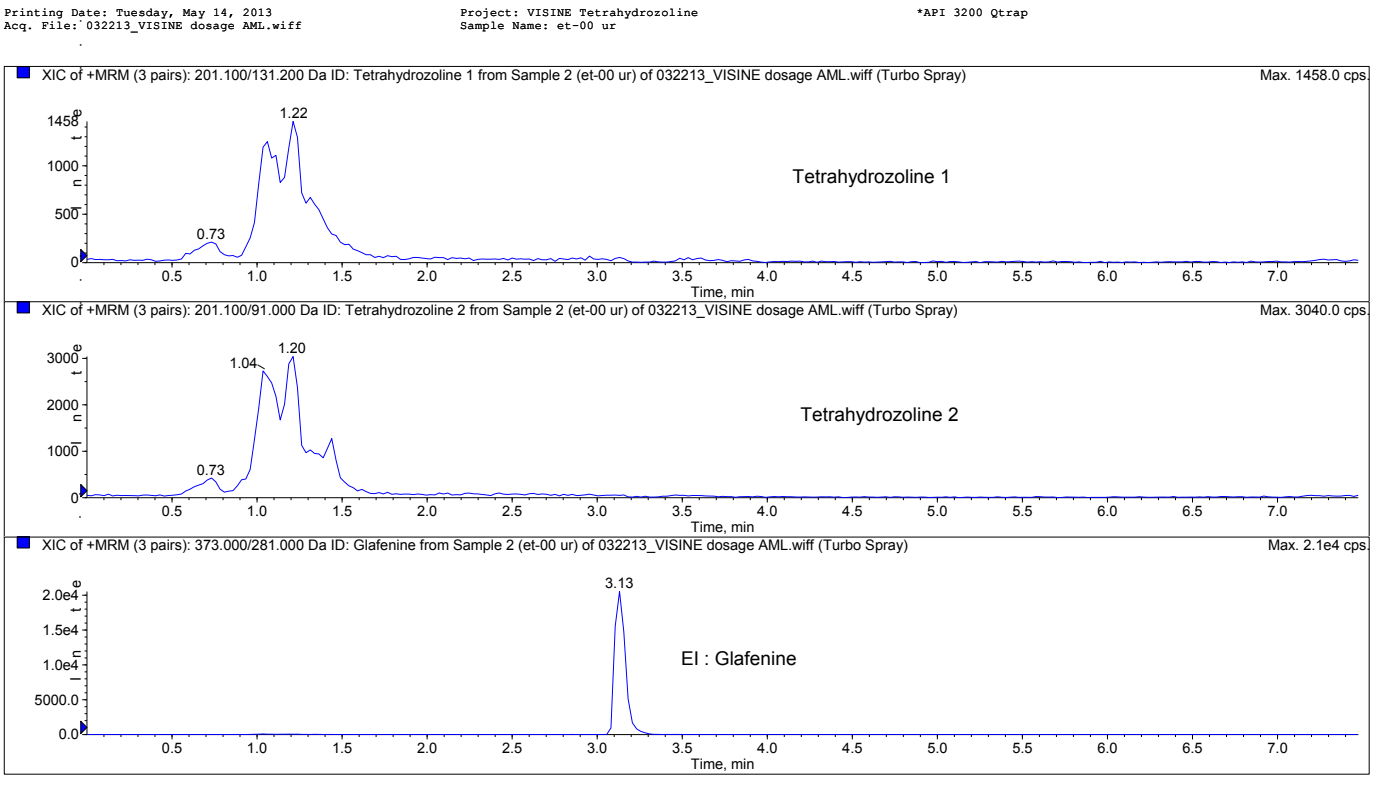


FIGURE 1 (ABOVE) MRM chromatogram of Blank urine specimen.

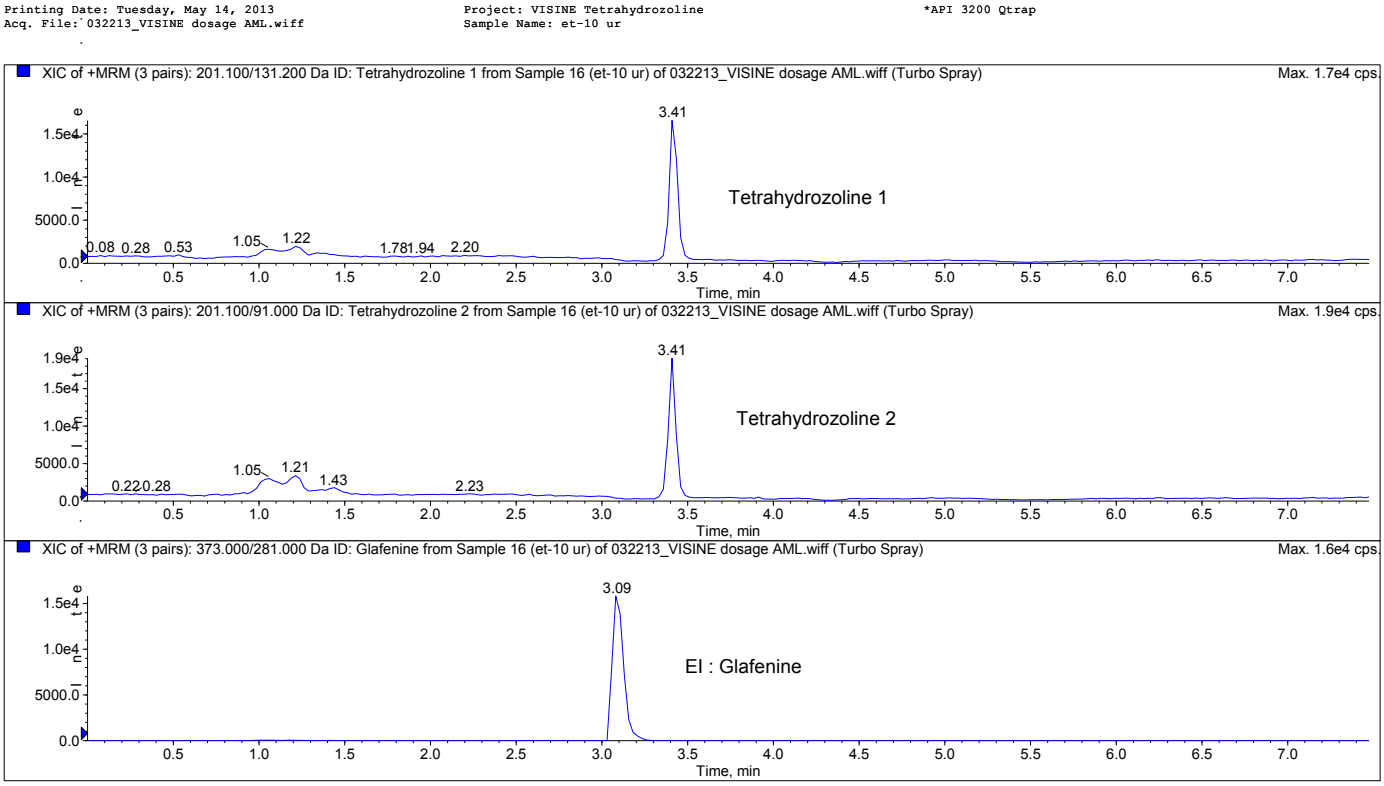
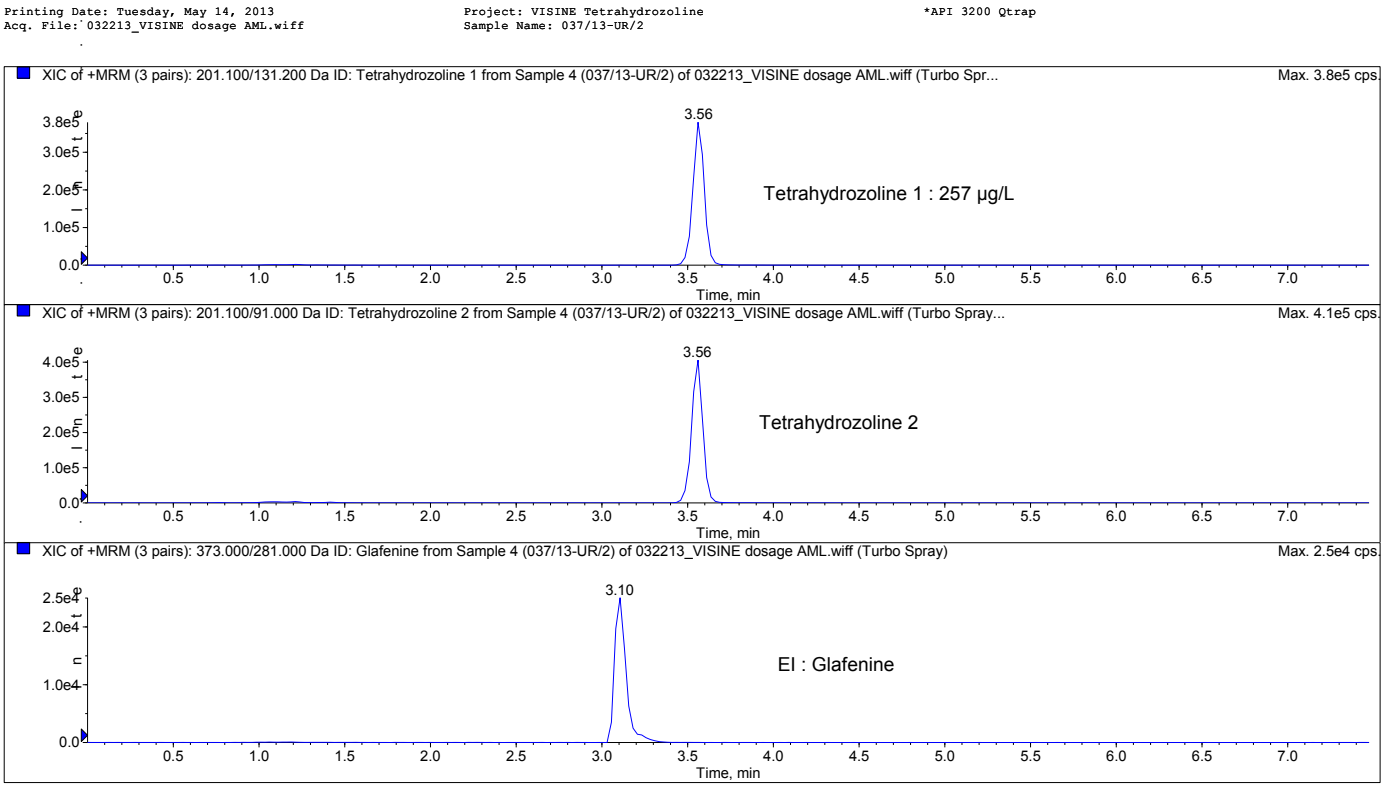


FIGURE 3 (ABOVE) MRM chromatogram of calibrator 10 ng/mL FIGURE 4 (BELOW) MRM chromatogram of specimen from the child (257ng/mL).



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