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CASE REPORT

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Car crash after massive ingestion of digoxin and midazolam

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Abstract In a case where a 32-year-old man lost control of his vehicle, urine and blood samples were taken 6 h after the crash for toxicological investigations. In the hospital, the driver admitted consumption of some drugs, in particular digoxin and midazolam just before the crash which corresponded to the results of blood analyses. Toxicological findings indicated the presence of digoxin at 12.9 ng/ml and midazolam at 7 ng/ml in the blood. These results suggested that at the moment of the crash digoxin and midazolam blood levels were in the range of toxic and therapeutic concentrations, respectively. Therefore the respective roles of the drugs in the impairment of the ability to drive at the moment of the crash is discussed.

Key words Digoxin · Midazolam · Driving under the influence of drugs (DUID) · Car crash

Introduction

In a recent Swiss study psychoactive drugs such as cannabinoids, opiates, ethanol, benzodiazepines and cocaine were the main substances found in biological samples from drivers suspected of driving under the influence of drugs (DUID) (Augsburger and Rivier 1997). However, other drugs were also reported in a few cases and the possible contribution of these drugs to driving impairment should always be carefully evaluated before coming to any conclusion.

Digoxin, like other cardiac glycosides has a powerful action on the myocardium, resulting in the use of these drugs for the treatment of heart failure. For a long time the use of digoxin has been a cause of contention, especially since the margin between therapeutic and toxic doses is very narrow. When cases of accidental and intentional digoxin poisoning have been reported (Baselt and Cravey 1995) no allusion to the influence of digoxin on driving has been given.

Midazolam, a benzodiazepine with a short half-life time, is used as a preoperative medication, sedative-hypnotic and anesthetic induction agent. Effects, in particular sleepiness, induced by this drug may impair driving ability (Hindmarch and Subhan 1983). Benzodiazepines have frequently been reported in cases of driving under the influence of drugs (Cirimele et al. 1996).

Case history

A 32-year-old man who was alone in his car, lost control of the vehicle which struck a wall at the end of a bend. The crash occurred during a sunny day. Due to unclear circumstances and indications of drugs (digoxin and midazolam) and alcohol consumption, toxicological analyses were ordered. Peripheral blood and urine samples were taken about 6 h after the crash. Medical examination revealed a somnolent behaviour, difficulties in speaking, dilated pupils and marked influence of drugs. Moreover, the patient was sleepy but always wakeable (Glasgow scale 14–15) and had frontal haematomas and a cutaneous wound on the chin. No typical signs of intoxication with digoxin were observed on the ECG. The patient did not remember what exactly had happened just before the crash.

During hospitalization, the patient indicated consumption of dibenzepine and bromazepam during the 3-month period before the crash because of a depressive state and he admitted occasional levothyroxine intake. The patient claimed that shortly before the crash he had ingested digoxin (400 pills of 0.25 mg !) and midazolam (200 pills of 15 mg !) together with red wine. He had vomited several minutes later, regretting what he had done. Then he felt so bad that he decided to drive to the nearest hospital and the crash happened during the journey.

Toxicological findings

The analysis of blood by headspace (HS) gas chromatography (GC) did not indicate the presence of alcohol. Urine was screened for drugs by immunoassays (DPC, CA) and the results suggested the presence of benzodiazepines in the urine. After liquid-liquid

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Table 1 Results of GC-MS analysis of urine and blood

Urine	Blood
midazolam	midazolam
1-hydroxy-midazolam	cotinine
nor-dibenzepine	caffeine
bis-nor-dibenzepine	
desalkyl-flurazepam	
hydroxy-lidocaine	
desethyl-lidocaine	
cotinine	
nicotine	
caffeine	

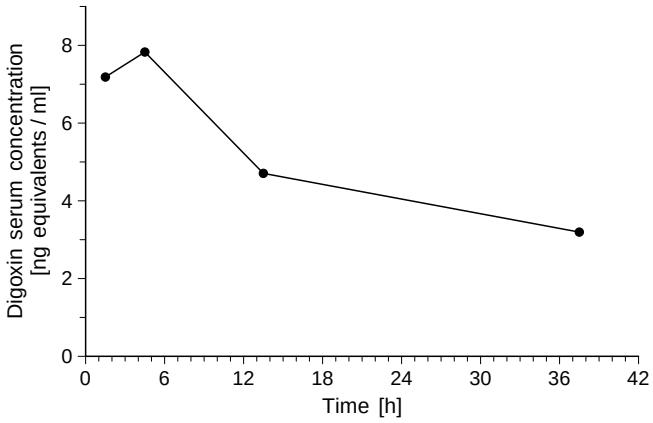

Fig. 1 Progress of the digoxin serum concentration during hospitalization. The crash occurred at time zero. Concentrations in serum were measured by immunoassay

extraction, blood and urine were screened by GC coupled to a mass spectrometer (MS) (HP 5971) allowing the identification of various drugs and/or metabolites in the urine and peripheral blood (Table 1) according to Pfleger et al. (1992). The results indicated the consumption of midazolam, dibenzepine, flurazepam, lidocaine (administered during hospitalization), nicotine and caffeine.

Digoxin was detected in the blood by radioimmunoassay (RIA digoxin, Coat-A-Count, DPC, CA) at a concentration higher than 8 ng/ml (highest calibrator concentration). Confirmation and quantitation of digoxin in the blood was done by high performance liquid chromatography (HPLC) coupled to MS (Perkin-Elmer Sciex API-100) by an ionspray interface (PE Sciex Ionspray), with oleandrine as internal standard (Tracqui et al. 1997). The results indicated the presence of digoxin in the blood at 12.9 ng/ml. The presence of digoxin was also suggested in the urine by radioimmunoassay at 2.0 µg equivalents digoxin/ml.

Monitoring of the digoxin concentration in serum by immunoassays (digoxin assay, VIDAS, bioMérieux, St. Louis, Missouri, USA) at the hospital showed an increase of the initial value during the first 4 h of hospitalization and a decrease over the following days (Fig. 1). Other blood parameters such as potassium and sodium were normal except for an increase of total concentration of creatine-kinase (from 191 UI/l on hospitalization to 327 UI/l 12 h later) which could be explained by the contusions and wounds received.

After liquid-liquid extraction, analysis by GC (HP 5890) coupled to an electron capture detector (ECD) (HP G1223A) allowed the quantification of midazolam (Ulrich und Sager 1988) showing a blood concentration of 7 ng/ml.

Discussion

The presence of midazolam and digoxin in the blood more than 6 h after the crash confirmed the driver's allegations concerning the consumption of these two substances. Nonetheless, the quantity of absorbed drugs claimed by the driver could not be confirmed since vomiting had occurred.

Midazolam is a short-acting benzodiazepine with hypnotic-sedative, anticonvulsant, anxiolytic and marked amnestic properties. Midazolam is rapidly absorbed, shows a high distribution rate into the brain and is quickly eliminated (half-life: 1.5–3.5 h) (Dundee et al. 1984). The pharmacokinetical interpretation of the results suggested that at the moment of the crash, shortly after drug ingestion, the driver was under the influence of midazolam, probably at therapeutic levels. Midazolam consumption could explain the symptoms described by the driver, policemen and medical staff. Moreover sleepiness induced by this drug could have been strengthened by the presence of residues of flurazepam and dibenzepine (or their effective metabolites) detected in the urine.

Digoxin is a well known cardiotonic plant glycoside used in the treatment of congestive heart failure. An optimal response is obtained at plasma concentrations between 0.5 and 2.0 ng/ml. Although it is difficult to give a serum level limit indicating intoxication, serum levels over 15 ng/ml usually correlate with serious intoxication (Ellenhorn and Barceloux 1988). After digoxin fatalities, blood or serum concentrations range from 3.5 to 200 ng/ml with an average of 25 ng/ml (Baselt and Cravey 1995). Digoxin is mainly eliminated by the kidneys and two-thirds of a single dose is excreted in the urine over a 7-day period, 95%–98% as unchanged drug. In cases of acute intoxication, patients develop nausea and vomiting, mental status changes may be present and cardiovascular symptoms are the most frequent effects (Ellenhorn and Barceloux 1988).

In the present case, the digoxin concentration in the blood measured by HPLC-MS was within the toxic range. The high level of digoxin found in the urine indicated that a substantial amount of digoxin had been already excreted at the moment of urine sampling. Nausea, vomiting, weakness, fainting and drowsiness were noted by the patient or observed after the crash by the police and medical examiner. Surprisingly, some typical toxic effects such as confusion, disorientation, delirium, xanthopia and scotoms were not observed as well as abnormal clinical cardiac parameters. Although no cardiac complications were observed, transitory cardiac arrhythmias involving fainting at the moment of the crash could not be positively excluded. Gastrointestinal problems, which occurred several minutes after ingestion could be ascribed to the high number (600) of tablets and to mucosa irritation or local reflexes provoked by digoxin. For these reasons it is very likely that digoxin did not play a substantial role in the impairment of the ability to drive at the moment of the crash, whereas it could easily be assumed that midazolam was the cause of the crash.

In conclusion, in cases of DUID a substance detected in toxic ranges is not necessarily the substance involved in the driving impairment. For this reason pharmacological interpretation of the results is a crucial step in the determination of driving impairment due to drugs.

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