Forensic Science International xxx (2015) e1–e6

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Case Report

Multi-drug intoxication fatality involving atorvastatin: A case report

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ARTICLE INFO

Article history:
Received 30 June 2015
Received in revised form 24 September 2015
Accepted 30 September 2015
Available online xxx

Keywords:
Antihypertensive
Hypolipidemic
Alcohol
Intoxication
Suicide
Rhabdomyolysis

ABSTRACT

Mixed antihypertensive drug intoxication poses a significant risk for patient mortality. In tandem to antihypertensives, hypolipidemic medicines (especially statins) are often prescribed. Among their well-known adverse effects belongs rhabdomyolysis. We report a case of fatal multi-drug overdose in a 65-year-old female alcoholic. The patient was unconscious at admission. Empty blister packs indicated the abuse of 250 tablets of urapidil, 42 tablets of verapamil/trandolapril, 50 tablets of moxonidin, 80 tablets of atorvastatin and 80 tablets of diacerein. Standard measures (gastric lavage, activated charcoal, mechanical ventilation, massive doses of vasopressors, volume expansion, diuretics and alkalinization) failed to provide sufficient drug elimination and hemodynamic support and the sufferer deceased on the fourth day. Dramatic elevations of serum myoglobin (34,020 μg/L) and creatine kinase (219 μkat/L) were accompanied by rise in cardiac troponin I and creatinine. Gas chromatography revealed ethanol 1.17 g/kg (blood) and 2.81 g/kg (urine). Thin layer chromatography and gas chromatography of gastric content and urine verified verapamil, moxonidin and urapidil fragment (diacerein method was unavailable). Atorvastatin and trandolapril concentrations (LC-MS^n) equaled 277.7 μg/L and 57.5 μg/L, resp. (serum) and 8.15 μg/L and 602.3 μg/L, resp. (urine). Histology confirmed precipitates of myoglobin with acute necrosis of proximal renal tubules in association with striated muscle rhabdomyolysis and myocardial dystrophy. Cardiogenic-distributive shock in conjunction with acute renal failure due to the combined self-poisoning with vasoactive agents and atorvastatin were determined to be this decedent's immediate cause of death. The manner of death was assigned to be suicidal.

1. Introduction

Antihypertensives and hypolipidemics belong among the most commonly prescribed drugs. Despite providing beneficial effects in terms of decreased long-term cardiovascular morbidity and mortality, these pharmaceuticals may pose a high risk of death, particularly when administered in parallel and when largely overdosed. Intoxications by one or more of these medications were documented in a number of case reports [1–9] and reviews [10,11].

The most noxious adverse effects of antihypertensives are due to arrhythmia and excessive vasodilation with hypotension, whereas the use of hypolipidemics (statins) is monitored to reduce the chance of the development of severe myopathy. The prescription of more antihypertensives (from various groups with different mechanisms of action) rather than escalating daily intake of a solitary drug is based on greater blood pressure-lowering capacity. Moreover, in the form of fixed combinations these preparations are becoming increasingly preferred by physicians also for reasons of patientś adherence to therapy especially in polypharmacy. This paper reports on an unusual case of fatal self-poisoning of an alcohol-dependent patient with multiple antihypertensive medicines and atorvastatin.

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http://dx.doi.org/10.1016/j.forsciint.2015.09.020
0379-0738/

2. Case report

2.1. Clinical summary

A 65-year-old chronic female alcoholic with a medical history of obesity, hypertension, hyperlipidemia, cholecystolithiasis and chronic vertebrogenic syndrome was admitted to the intensive care unit of a municipal hospital for unconsciousness. On the day before admission the diseased was examined at emergency department for alcoholic ebriety and was released home in the company of her husband. Following discharge, the patient managed to ingest high amounts of her usual medications. Empty blister packs indicated the abuse of 250 tablets of urapidil, 42 tablets of verapamil/trandolapril, 50 tablets of moxonidin, 80 tablets of atorvastatin and 80 tablets of diacerein (Table 1). On arrival the sufferer presented with Glasgow Coma Scale (GCS) score of 11/15, hypoventilation and hypotension (blood pressure 60/40 mmHg) with initially normal sinus rhythm (Fig. 1a). The condition deteriorated quickly and necessitated intensive care with the introduction of mechanical ventilation. Blood-, urine- and gastric lavage samples were taken for toxicology and standard therapy involving fluids and activated charcoal was initiated. The screening revealed ethanol in the blood and urine and verified or quantitated the presence of five out of six suspected generics in the blood, gastric content or urine (the method for the detection of diacerein was unavailable, Table 2). In an attempt to provide adequate drug elimination and hemodynamic support during the next three days the treatment of the inpatient included substantial doses of vasopressors, volume expansion, forced diuresis and alkalinization. In spite of this therapy the subject developed arrhythmia (Fig. 1b) and laboratory signs of multiple organ toxicity (Table 3) with progressive loss of renal function. Owing to massive atorvastatin-induced rhabdomyolysis and refractory cardiogenic-distributive shock the approach was ineffective in preventing acute renal failure resulting in death on the fourth day of hospitalization.

2.2. Analyses

Routine serum analytes were determined using Abbott Architect ci8200 clinical chemistry and immunochemistry analyzer and Advanced Micro Osmometer Model 3300 in compliance with the manufacturerś instructions. In addition to measurement, serum osmolality was calculated using the following formula: osmolality (mmol/kg) = $2 \times [Na^+]$ + [urea] + [glucose], where $[Na^+]$, [urea] and [glucose] represent serum concentrations (mmol/L) of sodium, urea and glucose, respectively. Serum and urine ethanol concentrations were determined using AutoSystem™ XL gas chromatograph (GC AS XL, PerkinElmer) with flame ionization detector (FID). Then corresponding concentration of ethanol in the whole blood was calculated from serum concentration.

To determine the concentration of atorvastatin and trandolapril in serum and urine samples LC-MS^n analyses were performed. The apparatus consisted of a Thermo Fisher Scientific LTQ XL liquid chromatograph-linear ion trap equipped with PAL autosampler, Rheos 2200 HPLC pump and electrospray ionization (ESI) source. We utilized a 7.5 cm × 2.1 mm, 2.7 μm Ascentis Express RP-Amide HPLC column (C18 phase) supplied by Supelco. The column temperature was maintained at 22 °C. As a mobile phase 5 mM formic acid with acetonitrile was employed under gradient conditions and at 220 μL/min flow rate. Nitrogen was used to assist nebulization. Atorvastatin method: the ESI source was set with sheath gas at 45 units, auxiliary gas at 9 units, spray voltage was set at 3.70 kV, capillary temperature at 275 °C, capillary voltage at −96 V and tube lens at −153.00 V. Trandolapril method: sheath gas was set at 55 units, auxiliary gas at 15 units, spray voltage at 4.0 kV, capillary temperature at 300 °C, capillary voltage at 29 V and tube lens at 121 V. For calibration purposes atorvastatin calcium salt trihydrate, trandolapril (both obtained from Sigma-Aldrich) and hydrochlorothiazide-3,3-d2 (internal standard, purchased from CDN Isotopes) were selected as standards.

To detect benzodiazepines and opiates in the native urine immunoassays were carried out on AxSYM (Abbott) platform. These results were negative.

Prior to verapamil, moxonidine and urapidil (metabolites) identification, liquid–liquid (L-L) extraction of these substances was effectuated as follows: 50 mL of urine were extracted with 2 × 50 mL diethyl ether under acidic (pH 1) and then under alkaline (pH 10) conditions to obtain UA (acidic) and UB (basic) fractions. Diethyl ether was evaporated to dryness using nitrogen at room temperature. The residue was dissolved in 1 mL of methanol. The detection was performed using UB fractions by thin layer chromatography (TLC) and confirmed also by GC-MS. The TLC (Silica gel 60 F254, Merck) procedure was employed with the Dragendorff solution, 1% (w/v) iodine solution in chloroform and 1% $Ce(SO_4)_2$ in 1 M H_2SO_4 as detection reagents. As for GC-MS, 1 μL of sample was injected in a splitless mode into the apparatus using helium (1.5 mL/min, constant flow-rate) as the carrier gas. The system consisted of Gas chromatograph Trace 2000 equipped with mass detector PolarisQ (Thermo Finnigan) and capillary column Rtx®-5MS (15 m length × 0.25 mm inner diameter × 0.25 μm film thickness, Restek). The injector temperature was set at 230 °C, the temperature of the transfer line heater was 280 °C. The temperature gradient was regulated in the following manner: 70 °C (for 1 min), 15 °C/min to final temperature 260 °C (sustained for 10 min). Mass spectra were collected between m/z 40 and m/z 450 with one scan per second. The electron ionization source temperature was adjusted to 200 °C, ionization energy to 70 eV and emission current to 250 μA.

Table 1
Overview of the drugs supposably taken by the patient.

Market drug name	Mass in one unit (tbl./cps.)	No. of units ingested	Expected total dose taken (g)	Generic name	Mechanism of action of the active component
Ebrantil® ret.	30 mg	250 cps.	7.5	Urapidil	Central sympathetic tone and peripheral postsynaptic α-1 receptor blocker
Tarka® 240/4	240 mg	42 tbl.	10.1	Verapamil	Calcium channel blocker
	4 mg	42 tbl.	0.17	Trandolapril	ACE-inhibitor
Moxogamma®	0.3 mg	50 tbl.	0.02	Moxonidin	Central I_1-imidazolin and α-2-adrenergic receptor stimulator
Tulip®	10 mg	80 tbl.	0.8	Atorvastatin	HMG-CoA inhibitor
Artrodar®	50 mg	80 cps.	4	Diacerein	IL-1β inhibitor

Please cite this article in press as: L. Cibickova, et al., Multi-drug intoxication fatality involving atorvastatin: A case report, Forensic Sci. Int. (2015), http://dx.doi.org/10.1016/j.forsciint.2015.09.020