AN AUTOPSY CASE OF CARBAMAZEPINE POISONING

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Abstract

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We present a case of fatal carbamazepine poisoning. Quantitative analysis of carbamazepine using high performance liquid chromatography, revealed that the concentrations of carbamazepine were 50.2 μg/ml in the femoral venous blood and 60.3 μg/ml in the heart blood, respectively, and many unabsorbed tablets were also observed in the stomach contents. We concluded that the cause of death was due to carbamazepine overdose.

Key words: carbamazepine – poisoning – high performance liquid chromatography

Souhrn

Pitevní nález otravy carbamazepinem

Autoři presentují případ smrtelné otravy carbamazepinem. Kvantitativní analýza otravy carbamazepinem vysoce výkonnou kapalinovou chromatografií stanovila koncentraci carbamazepinu v krvi z femorální žíly 50,2 μl/l, respektive 60,3 μg/l v krvi odebrané ze srdečního svalu, a mnoho nevstřebaných tablet bylo také nalezeno v žaludečním obsahu. Stanovili jsme, že příčinou smrti bylo předávkování carbamazepinem.

Klíčová slova: carbamazepin – otrava – vysoce výkonná kapalinová chromatografie

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INTRODUCTION

Carbamazepine, an iminostilbene derivative structurally related to the tricyclic antidepressants, is widely prescribed as an anticonvulsant and for the treatment of trigeminal neuralgia [1]. The major pharmacological action of carbamazepine is anticonvulsive, which is mediated by a slowing of the rate of recovery of voltage-activated Na^+ channels from inactivation [8]. Carbamazepine is the second most common overdose anticonvulsant in Japan and the United States, following valproic acid [4,17], but there are few reported fatal cases in Japan [11]. Here we report a case of death due to the toxicity of carbamazepine.

CASE REPORT

A Japanese 35-year-old male was found dead in his room. The subsequent police investigation revealed that the deceased had been receiving therapy for mental disorder and had been prescribed drugs.

The deceased was 178 cm in height and 75 kg in weight. No external evidence of violence was found. The heart weighed 390 g, contained 500ml of blood without coagulum. The brain weighed 1347 g and was slightly edematous. The left and right lungs weighed 555 and 586g, respectively, and were moderately congested. There were approximately 650 ml of stomach contents, containing foodstuffs and tablets (Figure 1). There were no notable changes, other than congestion in the other organs. A drug screening test using a Triage™ (Biosite Diagnostic Inc, San Diego, USA) panel was positive for barbiturates. Postmortem samples of heart blood, femoral venous blood, urine, cerebrospinal fluid and the stomach contents were collected for toxicological investigation.

Toxicological analysis was performed using a high performance liquid chromatography drug analysis system (Class-VP system, Shimadzu, Kyoto, Japan) [5]. The operation of this system was in accordance with the manufacturer's specifications. The quantitation of ethanol was performed using head-space gas-chromatography.

RESULTS AND DISCUSSION

Carbamazepine and Phenobarbital were identified by the toxicological examination. Phenobarbital, a barbiturate derivative, is widely used as a sedative and an anticonvulsant [2,8]. The concentrations in each postmortem specimen are presented in Table 1. No ethanol was detected in the blood

Table 1. Carbamazepine and phenobarbital concentrations in each sample.

Specimen	Carbamazepine (μg/ml)	Phenobarbital (μg/ml)
Heart blood	60.3	15.8
Femoral venous blood	50.2	14.8
Urine	9.43	34.0
Cerebrospinal fluid	16.2	8.39
Stomach contents	4984.9	70.3

and urine. The therapeutic range of plasma carbamazepine is 1.4-12 μg/ml, while a toxic level exceeds 15 μg/ml, and the concentration in fatal cases ranges over 50 μg/ml [18]. Clinically, severe poisoning symptoms in a patient with a concentration of over 40μg/ml have been reported [3]. In the present case, the concentration of carbamazepine (50.2 μg/ml) was within the fatal range, while the phenobarbital was within therapeutic levels (10-40 μg/ml) [2, 18]. In this case, it was apparent that the victim died during the absorption phase of carbamazepine following oral ingestion. This also supports the diagnosis of carbamazepine poisoning as the cause of death. Because the concentration of phenobarbital was within the therapeutic range, its contribution to his death may be small.

As shown in Table 1, the concentration of carbamazepine in the heart blood was about 1.2 times higher than in the femoral blood. This may be due to the concentration gradients in the absorption phase between the portal and the pheripheral vein [6,16] and/or postmortem diffusion from the stomach [13]. Because the concentration of carbamazepine in the stomach contents was approximately 100 times higher than in the femoral vein, due to large amounts of the drugs left in the stomach. This may be due to the strong anticholinergic action of carbamazepine itself, which inhibits stomach emptying and intestinal peristalsis, resulting in a delay in absorption and the onset of poisoning symptoms [15].

The carbamazepine concentrations in the cerebrospinal fluid was about 32.3% of that in the femoral venous blood. The brain is protected from the various kinds of xenobiotics by two anatomical barriers such as blood-brain-barrier (BBB) and blood-cerebrospinal fluid-barrier (BCB) [7]. It has previously been thought that BBB and BCB absolutely restricted the entry of drugs into the brain [7]. However, in a recent study, drug efflux transporters such as P glycoprotein (Pgp) and the multidrug resistance-associated protein (MRP) were seen to contribute to the passage of substances, such as carbamazepine, across the BCB, and Pgp and MRP were seen to reduce the drug concentration in cerebrospinal fluid [12, 14]. Neurological symptoms such as coma and seizures, have often been observed in carbamazepine overdose [15]. Therefore the concentration of carbamazepine in the cerebrospinal fluid may be useful for the evaluation of its severity.

We have also estimated the victim's total amounts of ingestion of carbamazepine and phenobarbital, using values of the distribution volume (Vd) for carbamazepine (1.4 L/kg) and phenobarbital (0.5 L/kg) [9, 10], the victim's body weight and femoral blood levels. The calculated amounts of carbamazepine and phenobarbital were approximately 5.2 and 0.55 g, respectively. In this case, however, the ingested amount of carbamazepine may have been larger than the estimated amount, because there were a lot of unabsorbed tablets of drugs remaining in his stomach. The total ingested dose of each drug is the sum of the above value and the dose left in the stomach. We therefore estimated that he had ingested at least 8.4 g of carbamazepine and 0.6 g of phenobarbital.

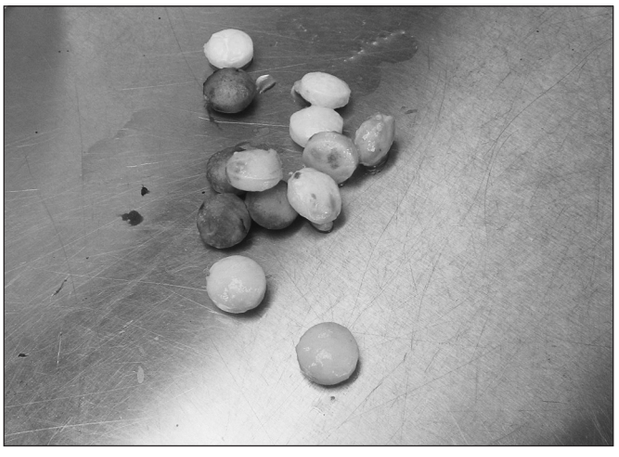

Figure 1. Tablets in the stomach.

From the autopsy findings, results of the toxicological examination, we conclude that the death was due to an overdose of carbamazepine.

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RECENZE

J. L. PILGRIM, D. GEROSTAMOULOS, O. DRUMMER: „DEATH INVOLVING SEROTONERGIC DRUGS". TIAFT BULLETIN 39/3, 2009, 20-25.

Jennifer Pilgrim je PhD studentkou ve 3. ročníku na Ústavu forenzní mediciny na Univerzitě Monash, Melbourne, Victoria, Austrálie. V souhrnném článku pojednává o1123 fatálních případech ve státě Victoria během let 2002–2008, kde byly prokázány serotonergní substance tramadol, venlafaxin, fluoxetine, sertraline, citalopram, paroxetine a MDMA. Se zřetelem na patologii, toxikologii a anamnestické údaje byla tato úmrtí zkoumána s cílem zjistit, zda uvedené serotonergní látky mohly způsobit náhlou smrt. Diagnóza serotoninového syndromu (SS) podle Sternbachova kritéria zahrnuje klinické příznaky jako změny psychického stavu, neklid, záškuby svalstva, chvění a třes, pocení, hyperreflexii. Posuzované případy jsou kategorizovány do 5 skupin podle příčiny úmrtí.

(H. Sternbach, The Serotonin Syndrome. Am. J. Psychiatry, 148, 1991, 705-713)

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