An autopsy case of multiple psychotropic drug poisoning

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SUMMARY
A fatal poisoning case involving etizolam, phenobarbital, promethazine and chlorpromazine is presented. Quantitative toxicological analysis showed that the concentrations of etizolam, phenobarbital, promethazine and chlorpromazine in the femoral blood were 86 ng/ml, 5,082 μg/ml, 0,107 μg/ml and 0,144 μg/ml, respectively, and large amounts of drugs were also detected in the stomach contents. We conclude that the cause of death was due to the interaction of multiple psychotropic drugs.

Keywords: multiple drug – poisoning – high performance liquid chromatography – etizolam – phenobarbital

Pitva při otravě četnými psychotropními léky

SOUHRN
Prezentován je případ smrtící otravy etizolamem, phenobarbitalem, promethazinem a chlorpromazinem. Kvantitativní toxikologická analýza prokázala, že koncentrace v krvi odebrané ze stehenní žíly dosahovala u etizolamu 86 ng/ml, phenobarbitalu 5,082 μg/ml, promethazinu 0,107 μg/ml a chlorpromazinu 0,144 μg/ml, přičemž velké množství léků bylo také zjištěno v obsahu žaludku. Uzavřeli jsme, že příčina smrti byla v souvislosti se vzájemným působením četných psychotropních léků.

Klíčová slova: četné léky – otrava – vysokoúčinná kapalinová chromatografie – etizolam – phenobarbital

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Cases of poisoning due to multiple psychotropic drug ingestion are large problems in the fields of forensic toxicology, because the interactions of the various drugs are complicated. Etizolam, which is a thenotriazolodiazepine derivative, has been used as a sedative-hypnotic drug (1), but there are few reported fatal cases due to the use of etizolam (2). Phenobarbital, a barbiturate derivative, is widely used as a sedative and as an anticonvulsant (3). The major pharmacological action of phenobarbital is an anticonvulsive effect, which results from synaptic inhibition through action on the $GABA_A$ receptor (4). Both promethazine and chlorpromazine are phenothiazine derivative. Promethazine is used as a sedative, and it also has antihistaminic and antiemetic effects (5). Chlorpromazine is widely used in the treatment of psychotic disorders (6). Here we report on a case of death involving the toxicity of multiple psychotropic drugs.

CASE REPORT

A Japanese 42-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 was receiving prescribed drugs.

The deceased was 169 cm in height and 101 kg in weight. The heart weighed 389 g and contained 580 ml of blood with coagulum. The brain weighed 1347 g and was slightly edematous. The left and right lungs weighed 489 g and 663 g, respectively, and were congested. There were approximately 100 ml of stomach contents, which included granules. There were no notable changes, other than congestion, in the other organs. Drug screening test using a Triage™ (Biosite Diagnostic Inc, San Diego, USA) panel was positive for barbiturates and benzodiazepines. Postmortem samples such as femoral venous blood, urine 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) (7). The system was operated in accordance with the manufacturer's specifications. Quantitation of ethanol was performed using head-space gas-chromatography.

RESULTS AND DISCUSSION

Toxicological analysis identified etizolam, phenobarbital, promethazine and chlorpromazine, but no ethanol was detected in the blood or urine. Table 1 shows the quantitation of etizolam, phenobarbital, promethazine and chlorpromazine in the victim's blood, urine and stomach contents, and also summarizes their fatal and therapeutic levels (8–12). In this case, it was apparent that the victim died during the absorption phase following oral ingestion,

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Table 1. Drug concentrations in each sample (μg/ml or μg/g) and their fatal and therapeutic levels.

Specimen	Etizolam	Phenobarbital	Promethazine	Chlorpromazine
Femoral blood	0,086	5,082	0,107	0,144
Urine	N.D.	1,736	0,806	1,437
Stomach contents	34,4	5480	1534	1708
	(3.4)*	(548)*	(153)*	(171)*
Therapeutic levels in blood	<0.025 (8,11)	4.5-24.3 (10)	0.006-0.099 (12)	0.01-0.5 (12)
Fatal levels in blood	?	2-239 (9)	2.4-12 (12)	3-12 (12)
N.D.: Not detected.				

* Each figure in parentheses represents the total amount of drug in the stomach (mg).

based on the detection of the quite high concentrations and large amounts of drugs in the stomach.

The blood concentration of etizolam exceeded therapeutic levels (8,11). Since etizolam is a relative safe drug, only a small number of fatal cases have been reported (2). The maximum plasma concentration of etizolam was 8,3 ng/ml following a 0,5 mg oral dose (8), or 25 ng/ml after an oral dose of 2 mg, and its toxic level range is 20–100 ng/ml (11). In the present case, the concentration of etizolam was within toxic levels.

There is a considerable overlap between the fatal and therapeutic levels of phenobarbital. Therapeutic plasma levels for phenobarbital are 4,5–24,3 μg/ml (10), while blood concentrations in fatal cases have been reported at a range of 2-239 μg/ml (10). In the present case, although the concentration of phenobarbital was within therapeutic levels (4,5–24,3 μg/ml) (10), its contribution to the fatality may not be small.

Both barbiturates and benzodiazepines act on the $GABA_A$ receptor site. Barbiturates enhance the benzodiazepine binding (4), and potentiate its pharmacological action. If depressant drugs are present, as in the present case, the fatal concentration level becomes lower (4). In the present case, the combined use of etizolam and phenobarbital may potentiate a poisonous adverse effect such as CNS depression. Since blood levels of promethazine and chlorpromazine were both within therapeutic ranges (12), these drugs may be less contributed to his death.

We have also estimated the victim's total amounts of ingestion of etizolam, phenobarbital, promethazine and chlorpromazine, using forensic toxicokinetic factors (13). The calculated amounts of etizolam, phenobarbital, promethazine and chlorpromazine, using values of the distribution volume (Vd) for etizolam (0,9–1,0L/kg), phenobarbital (0.5L/kg), promethazine (13L/kg), and chlorpromazine (21L/kg) (14–17), the victim's body weight and blood levels, were approximately 8,6mg, 256mg, 135mg and 305mg, respectively. In this case, however, the ingested amount of each drug may have been larger than the estimated amount, because 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 12mg of etizolam, 804mg of phenobarbital, 288mg of promethazine and 476mg of chlorpromazine, respectively.

From the autopsy findings and the results of the toxicological examination, we conclude that death was due to the interaction of multiple psychotropic drugs. We have only a small amount of data concerning the effects of drug interaction in case of multiple drug use. The present case indicates that we should pay more attention to the toxicity of combinations and interactions of the multiple psychotropic drugs.

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