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SUICIDE ATTEMPTS WITH TRICYCLIC ANTIDEPRESSANTS

TRİSİKLİK ANTİDEPRESANLARLA İNTİHAR GİRİŞİMLERİ

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ABSTRACT

Tricyclic antidepressant drugs (TCA) are the second widely used drugs after the analgesics, and involve in acute poisoning cases. In this study we measured unusual high dose of TCA levels in three suicidal poisoning cases. Toxicological screening on patients urine and blood samples were performed with GC/MS, and the quantitation of drugs were done with GC/MS and FPIA methods. Amitriptyline, acetaminophen, and codeine levels were 1135 ng/ml blood, 14.42 µg/ml blood, and 72.9 µg/ml urine respectively in case 1. Amitriptyline levels were found as 505, 429, and 370 ng/ml blood for consequent three days. In Case 2, amitriptyline levels were 883.56 and 137.35ng/ml blood for two days. In Case 3, initial imipramine level was 2560 ng/ml blood. First two patients were fully recovered 4 days after the incident. The third patient died 36 hours after the admission. In acute poisoning cases, early emergency teratment, obtaining rapid and reliable toxicological laboratory results were considered vitally important in poisoning cases.

Key words: *Tricyclic antidepressants, codeine, acetaminophen, GC/MS, FPIA*

ÖZET

Trisiklik antidepresanlar (TCA) analjeziklerden sonra en yaygın kullanılan ve sıklıkla akut zehirlenmelere neden olan ilaçlardır. Bu çalışmada üç intihar amaçlı zehirlenme vakasında hastaların idrar ve kan örneklerinde toksikolojik tarama testleri GC/MS ve FPIA metodları ile yapıldı. Birinci vakada ilk gün amitriptilin, asetaminofen ve kodein seviyesi sırasıyla 1135 ng/ml serum, 14.42 µg/ml serum ve 72.9 µg/ml idrar,takibeden üç günde ise amitriptilin düzeyi 505, 429 ve 370 ng/ml serum olarak ölçüldü. İkinci vakada,

1. ve 2. gün amitriptilin seviyesi 883.56 ve 137.35 ng/ml serum olarak, üçüncü vakada ise imipramin düzeyi 2560 ng/ml serum olarak ölçüldü. Birinci ve ikinci vakalar 4 gün içerisinde tamamen iyileşirken üçüncü hasta 36 saat sonra hayatını kaybetti. Akut zehirlenmelerde acil tedavinin erken ve toksikolojik analizlerin de güvenilir ve hızlı yapılmasının hayati derecede önemli olduğu gösterilmiştir.

Anahtar Kelimeler: *Trisiklik antidepresanlar, Kodein, Asetaminofen, GC/MS, FPIA*

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INRODUCTION

Suicidal attempts with multiple drugs are the most dangerous acute poisonings. Evaluations of physical findings of the patients are difficult because of the different kinds of high dose drugs. Acute poisoning symptoms of the central nervous system depressant and stimulant drugs are characteristic when they are taken separately (1). On the other hand, mixed drug poisonings are far more difficult from the single drug poisonings for the patient clinical symptoms evaluations. In those cases, emergency therapeutic attempts consist of the supportive and symptomatic therapies. Rapid toxicological analysis is essential for the identification of the involved poisons. Therefore, screening tests have to be performed in the biological samples (i.e. urine and blood). If the screening tests reveal any drugs or toxic substances, quantitative tests have to be done and the clinicians have to be informed immediately (2). Urine or blood levels of the poisons indicate the severity of the poisonings. Although immunological screening tests are fast and simple, they measure only a group of drugs. Obtained positive test results have to be confirmed with other tests, such as GC or GC/MS.

In acute poisoning cases, deaths from antidepressants continue to account for a substantial proportion of drug-related deaths (3). There are indications from large studies that maprotiline and amitriptyline might raise the suicide attempt rate, compared with placebo or other antidepressants, independent of their inherent toxicity in overdose (4). Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998-2000, were reported that most deaths from antidepressant drugs were suicides (80%). Tricyclic antidepressants (TCAs) accounted for more drug mentions than did other antidepressant drugs (12 per million prescriptions). Selective

serotonin reuptake inhibitors (SSRIs) were associated with a significantly lower risk of toxicity, but 93% of deaths from SSRIs occurred in combination with other drugs, especially TCAs (24.5%). Drug overdose is also a common method of suicide in the elderly (5). Paracetamol, co-proxamol, tricyclic antidepressants and benzodiazepines should be prescribed with caution to the elderly with depression or at high risk of depression (6).

In this research, we presented high dose fatal and non-fatal acute poisoning with tricyclic antidepressant drugs as a single drug or mixed type drug poisoning. We wanted to stress the importance of toxicological screening tests for both immunological (FPIA) and chromatographic (GC/MS) methods in any poisoning cases.

MATERIALS AND METHODS

Patients:

Case 1. A male soldier 23 years old was found in unconscious state at the backyard of hospital at 6 pm. He was immediately taken to the emergency department. Intravenous line was opened and given multiple electrolyte solution. Thiamine of 100 mg, 50 ml of 50% Dextrose, and 1 mg of Naloxone were also given initially via iv route. In order to protect gastric mucosal barrier, 40 mg omeprazole was also administered intravenously for the daily basis. Blood and urine samples were taken for the toxicological analysis. On physical examination, the patient was comatose, but the vital signs were normal except pupils, which were mildly constricted and unreactive to light stimuli. The patient's initial vital signs were blood pressure 121/65 mm Hg, pulse rate 99 beats/min, temperature 36.6 ^{o}C. Laboratory results including hemoglobin, glucose, urea, creatinine, sodium, potassium, SGOT, SGPT, arterial blood gases were given in Table 1. Toxicologic screening tests were performed on the patient's urine and blood samples. Rapid toxicological screening tests showed that blood and urine samples were positive for amitriptyline, codeine and acetaminophene. Quantitative analyses were applied for acetaminophene and amitriptyline on blood sample by fluoresceine polarization immunoassay (FPIA) technique. Codeine was detected and quantitated by gas chromatography/mass spectrometry (GC/MS) method in urine sample.

Case 2. A male soldier 22 years old was brought to emergency department at 7.30 am. It was said that he had taken approximately 15 tablets (25 mg amitriptyline/tablet) of Laroxyl (Roche Mustahzarlari, Istanbul, Turkey) for suicidal attempt a couple of hours before. His initial examination showed that he was unconscious, disoriented, and cardiac and pulmonary functions were normal. Intravenous line was opened and given multiple electrolyte solution and 40 mg

omeprazole. Gastric lavage and active charcoal administration were also performed. The patient's initial vital signs were blood pressure 101/59 mm Hg, pulse rate 92 beats/min, temperature of 36^{o}C. Laboratory results including hemoglobin, glucose, urea, creatinine, sodium, potassium, SGOT, SGPT, arterial blood gases were given in Table 2. Prior toxicological screening test with FPIA on patient's blood samplee was performed. When the test result was positive for TCA drugs, later toxicological screening tests were performed on the patient's urine and blood samples by GC/MS method. TCA drug was confirmed in both urine and blood samples as amitriptyline. Further urine and blood amitriptyline quantitation was not performed.

Case 3. Reportedly, a female 17 years old patient was brought to the emergency department of a local hospital with a history of suicidal ingestion of 100 tablets (25 mg imipramine/tablet) and 50 tablets (10mg imipramine/ tablet) of Tofranil (Novartis Saglik, Gida ve Tarim Urunleri San ve Tic AS, Istanbul, Turkey) with a cardiopulmonary arrest. On examination, her vital signs were absent. Cyanosis, dilated and fixed pupils, and no response to pain stimuli were also noted. She was immediately resuscitated. Gastric lavage and activated charcoal were also performed. The patient was transported to the Medical Intensive Care Unit of Gulhane Military Medical Academy 13 h later from the incident. The patient's blood pressure 64/38 mm Hg, pulse rate 96 beats/min, body temperature of 31^{o}C were recorded. She was mechanically ventilated, and her blood pressure was maintained with saline and dopamine. Laboratory test results including hemoglobin, glucose, urea, creatinine, sodium, potassium, SGOT, SGPT, arterial blood gases were given in Table 3. As in Case 2, prior toxicological screening test was performed on patient's blood with FPIA, and was found positive for TCA drug. TCA drug was later confirmed with the GC/MS method in both blood and urine samples.

Drug Screening in Blood and Urine Samples:

Urine samples were hydrolized with beta-glucuronidase (Sigma), and extraction procedures were performed at acidic, neutral and basic pH with ethyl acetate: heptane (1:1 v/v). Drug screening tests were carried out using gas chromatography-mass spectrometry (Shimadzu QP5050A) with a capillary DB-5 column (length, 30 m; 0.20 □m internal diameter; 0.33 mm film thickness) (J&W Scientific). The oven temperature was held at 55°C for 1 min and raised up to 150 °C at 20 °C/min and maintained at this temperature for 3 min. It was then programmed to 250 °C at 30 °C/min and maintained at this temperature for 12 min. The temperature of the injection port and interface were set at 280°C. Helium was used as a carrier gas (column inlet pressure 100 kPa, total

flow rate 30 ml/min). The mass spectrometer was operated under electron impact (EI) mode at ionization energy of 70 eV. One microliter of the sample was injected in splitless mode. Mass spectrometer was operated with a scan mass range of 40 to 350 atomic mass units (AMU) (7). Tricyclic antidepressants and acetaminophene were quantitated with FPIA with TDx (Abbott) (8). Codeine level was quantitated with GC/MS method.

RESULTS

Laboratory results of patients including hemoglobin, glucose, urea, creatinine, sodium, potassium, SGOT, SGPT, arterial blood gases were given in Table 1, 2 and 3. Toxicologic screening tests were performed on the patients' urine and blood samples. Rapid toxicological screening tests showed that blood and urine samples taken from Case 1, were positive for amitriptyline, codeine and acetaminophene (Figure 1and 2). In case 2, amitriptyline, and in Case 3, imipramine were detected in blood and urine samples (Figure 3). Quantitative analyses were applied for acetaminophene and amitriptyline in blood samples by FPIA and codeine was quantitated by GC/MS method in urine sample.

Table 1. Laboratory results of Case 1.

Laboratory Analysis	**Initial**	**2nd Day**	**3rd Day**
Blood glucose	84 mg/dl	73 mg/dl	80 mg/dl
Urea	14 mg/dl	20 mg/dl	25 mg/dl
Creatinine	1 mg/dl	1 mg/dl	0.9 mg/dl
Hemoglobin	12.5 g/dl	12.9 g/dl	12.6 g/dl
Sodium	132.4 mEq/L	134.9 mEq/L	134.6 mEq/L
Potassium	4.1 mEq/L	4.59 mEq/L	3.91 mEq/L
SGOT	13 U/L	14 U/L	11 U/L
SGPT	17 U/L	17 U/L	14 U/L
Arterial blood pH	7.48	NA	NA
pCO_2	28.8 mm Hg	NA	NA
pO_2	65 mm Hg	NA	NA
Amitriptyline*	1135 ng/ml blood	505 ng/ml	429 ng/ml
Acetaminophen*	14.42 µg/ml blood	BDL	BDL
Codeine**	72.9 µg/ml urine	BDL	BDL

NA: Not available, BDL: Below the detection limit, *Results from FPIA , **Results from GC/MS.

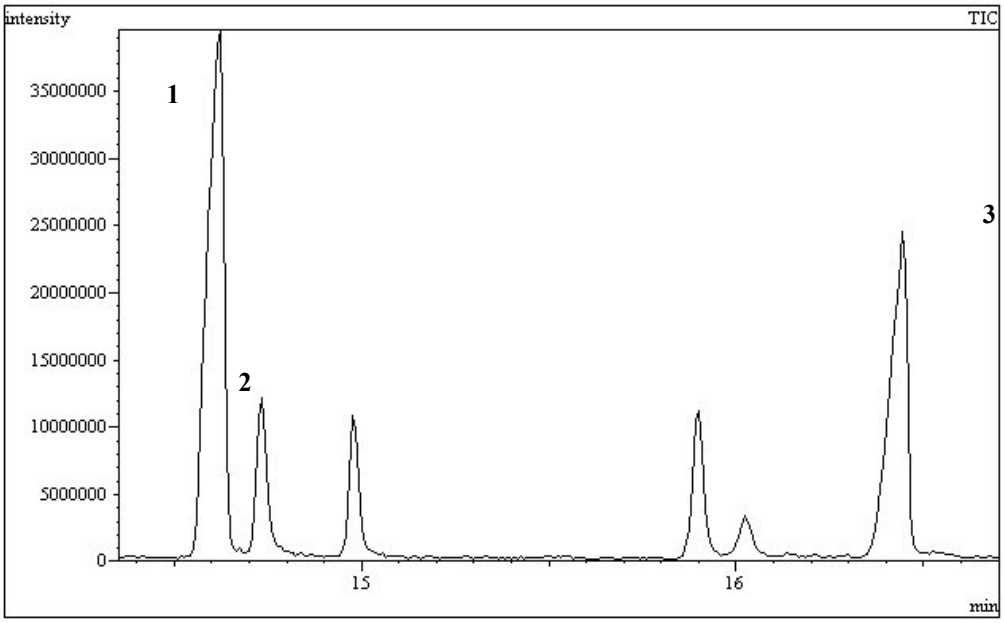

Figure 1. GC/MS chromatogram obtained from Case1 urine sample non-hydrolized basic extract. Peaks appeared at 14.617 min (peak 1) is amitriptyline, 14.725 min (peak 2) is nortryptiline, and 16.433 min (peak 3) is codeine.

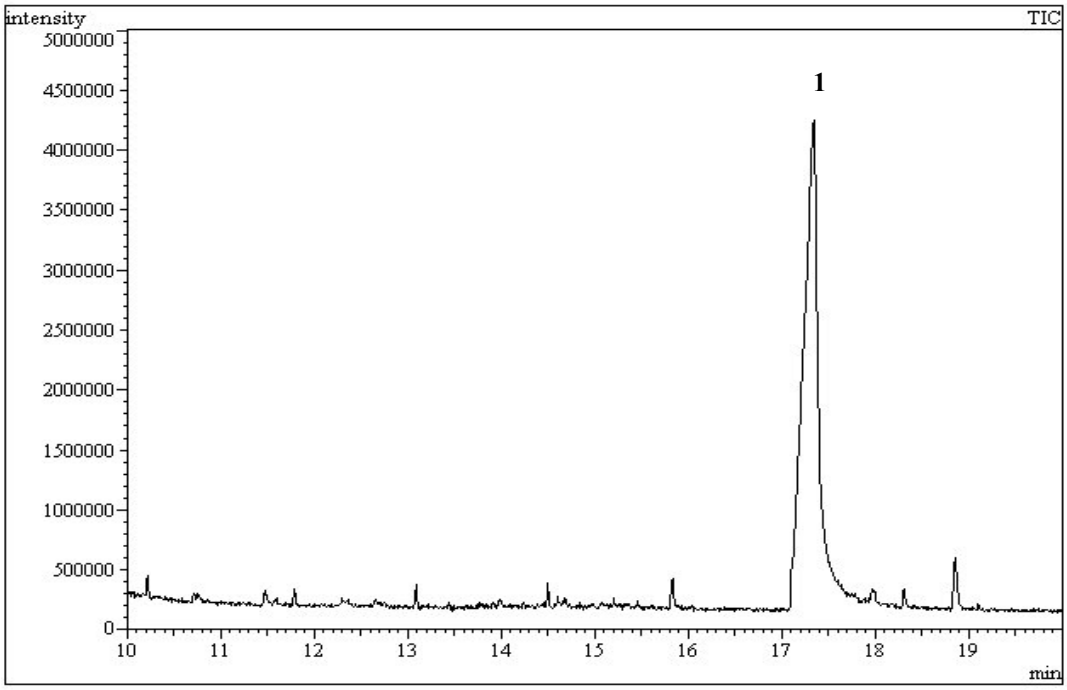

Figure 2. GC/MS chromatogram obtained from Case 1 urine sample hydrolized basic extract. Peak appeared at 17.342 min (peak 1) is acetaminophene.

Table 2. Laboratory results of Case 2.

Laboratory Analysis	**Initial**	**2nd day**	**3rd day**
Blood glucose	128 mg/dl	101 mg/dl	90 mg/dl
Urea	17 mg/dl	12 mg/dl	17 mg/dl
Creatinine	0.63 mg/dl	0.7 mg/dl	0.8 mg/dl
Hemoglobin	15 g/dl	13.5 g/dl	13.6 g/dl
Sodium	143 mEq/L	134 mEq/L	130.6 mEq/L
Potassium	4.3 mEq/L	3.16 mEq/L	3.67 mEq/L
SGOT	16 U/L	10 U/L	10 U/L
SGPT	11 U/L	12 U/L	9 U/L
Arterial blood pH	7.48	7.50	7.47
pCO_2	37.4 mm Hg	28.6 mm Hg	3.4 mm Hg
pO_2	37 mm Hg	65 mm Hg	62 mm Hg
Amitriptyline*	883 ng/ml blood	137 ng/ml blood	BDL

BDL: Below the detection limit, *Results from FPIA

Table 3. Laboratory results of Case 3.

Laboratory Analysis	**Initial**	**2nd Day**
Blood glucose	88 mg/dl	247 mg/dl
Urea	46 mg/dl	54 mg/dl
Creatinine	1.2 mg/dl	1.2 mg/dl
Hemoglobin	13.6 g/dl	NA
Sodium	142 mEq/L	140 mEq/L
Potassium	3.15 mEq/L	3.66 mEq/L
SGOT	467 U/L	501 U/L
SGPT	247 U/L	180 U/L
Arterial blood pH	7.54	7.28
pCO_2	20.7 mm Hg	49.6 mm Hg
pO_2	103 mm Hg	61 mm Hg
Imipramine*	2560 ng/ml blood	NA

NA: Not available, *Result from FPIA

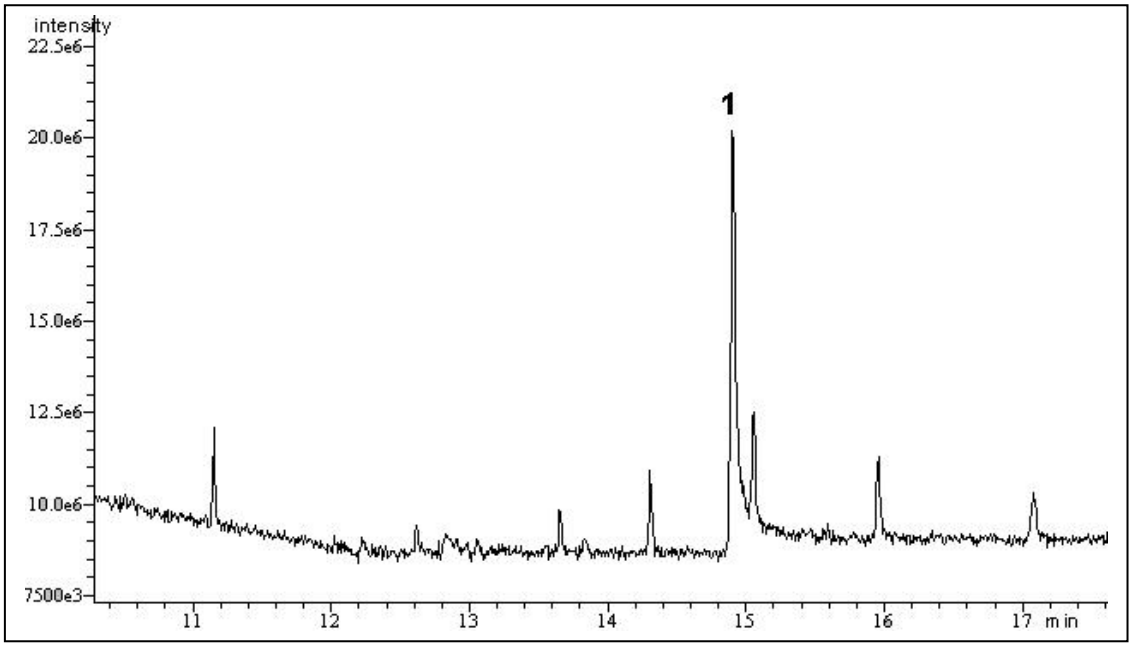

Figure 3. GC/MS chromatogram obtained from Case 3 urine sample hydrolized basic extract. Peak appeared at 14.908 min (peak 1) is imipramine.

DISCUSSION

The commonest prescription indication for TCAs is mood disorders, the condition most often associated with suicide. About half of the patients who commit suicide are depressed (2). According to the RSHM Poison Control Center reports, the most frequently seen poisoning cases with pharmaceuticals were TCA drugs originated (9). The biggest increase in the use of antidepressants in 1990-2000 has been in the 15 – 44 age group. Simultaneously the rate of suicide for this age span has increased in Australia. For men aged 25-34 the use of antidepressants has increased more than six times during the period and the suicide rate has increased by almost 17% (10). Among the suicidal intoxications in Sweeden, selective serotonin reuptake inhibitors (SSRI) and TCA were detected in 12% and 10% respectively. A significantly higher proportion of cases (64%) where TCA were detected had toxic concentrations when compared with cases where SSRI were detected (31%) (11). Treatment of a greater proportion of mood disorders with SSRIs and other second-generation non-tricyclic antidepressants may reduce the suicide rate (12). There were 200 poisoning deaths recorded in the database for New Zealand in 2001. Antidepressants were involved in 41 deaths, and death was attributed to an antidepressant in 23 cases. There were 5.52 deaths per 100 000 prescriptions for TCA and 2.51deaths per 100 000 prescriptions for SSRI (13).

Amitriptyline and imipramine are the first generation TCA drugs, which have been prescribed since 1950s. Suggested amitriptyline and imipramine therapeutic ranges are 80-250 ng/ml and 150-250 ng/ml blood respectively. Patients with plasma TCA levels greater than 450 ng/ml, tend to develop cognitive or behavioral toxicity (14). Ingestion of a dose of TCA greater than 20 mg/kg is generally considered potentially lethal. Survival after ingestion of as much as 10 g, and death from ingestion of as little as 500 mg of amitriptyline have been reported (1,15).

Acetaminophen is a widely used analgesic drug. The plasma half-life of acetaminophen is 1.25 to 3 hours, but may be increased by liver damage and following overdose. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 g, or fatalities with less than 15 g (16,17).

Codeine is one of the most effective antitussive narcotic analgesic drugs. Thus, codeine can be used alone or combined with other analgesics and decongestants. The half-life of codeine in plasma is 2.5 to 4 hours (18,19). As a cough suppressant, codeine phosphate is used 15 to 30 mg 3 to 4 times a day. Not more than 120 mg/day is recommended (20). The adult lethal dose is 0.5 to 1.0 g (21). This dose may cause convulsions and unconsciousness, and death from respiratory failure may result within 4 hours. Moffat et al. estimated the minimum lethal adult dose as 800 mg (18). Drug concentrations in codeine fatalities are approximately 2.8 mg/l in blood and 103.8 mg/l in urine (22).

In our presented Case 1, the patient had a history of 8 years cocaine usage. Last two years, he was taking amitriptyline HCl (25 mg/tablet) or opipramol HCl (50 mg/tablet) 6-9 tablets/day because of his anxiety problem without a doctor control. The patient claimed that he had taken approximately 30 tablets of Laroxyl, and 30 capsules of A-ferin (Bilim/Husnu Arsan Ilac San ve Tic AS, Istanbul, Turkey) containing 300 mg paracetamol, 2 mg chlorpheniramine maleate, and 10 mg codeine phosphate /capsule for suicidal attempt. In other words, he had taken 750 mg amitriptyline HCl, 9000 mg paracetamol, 60 mg chlorpheniramine maleate, and 300 mg codeine phosphate. Patient's claim seems to be correlated with the toxicolocical laboratory findings (Table 1). Initial drug levels were measured for amitriptyline 1135 ng/ml blood, for acetaminophen 14.42 µg/ml blood, for codeine 72.9 µg/ml urine. According to Rumack-Matthew nomogram, measured blood acetaminophen level was below the hepatotoxic concentration (1). Codeine and acetaminophen levels were below the detection limits on day 2nd (Table 1). Since the plasma half-life of these two drugs were considerably low comparing with TCA drugs (16-19). The patient was conscious, oriented and cooperated in 24 hours period. On the fourth day, the patient was transferred to the psychiatry department. According to the detailed literature search, this poisoning

case might be the first reported amitriptyline, acetaminophene and codeine multidrug poisoning case. The amounts of active ingredients of amitriptyline, paracetamol and codeine, were considerably higher than the therapeutic doses. Acute effects of these drugs might have been different from taken alone or with the presence of other drugs. Thus, initial examination was not specific for any ingested active ingredients except mild pupil constriction due to codeine.

In Case 2, initial and second day blood amitriptyline levels were 883.56 ng/ml and 137.35 ng/ml respectively by FPIA method. According to our experiences, this drug level might also be considered as a potential hazardous toxic exposure. In Cases 1 and 2, patients were gained their consciousness within 24 h, and fully recovered at 4 days after the incident. On the day fourth, each patient's health status was consultated with psychiatry department and discharged from the hospital. In Case 3, FPIA screening with TCA specific kits, 2560 ng/ml blood TCA drugs was measured. It was extremely high when compared 150-250 ng/ml blood therapeutic levels (14,23,24). TCA drugs consist of group of drugs having similar chemical structures. When we applied to GC/MS method, results indicated that causative drug was imipramine in this poisoning case. Although early emergency care intervention, the patient died 34 hours after the suicidal drug intake.

In acute poisoning cases, rapid toxicological analyses are vitally important for rational therapy. For the biological specimens toxicological screening, immunological screening tests such as FPIA, if available, might be preferred. The second steps of analytical procedures have to be applied for more detailed information about involved poison(s).

Since, evaluation and the treatment of mixed type acute poisoning cases are difficult to handle, early treatment and the rapid toxicologic analysis increase the success of treatment and rational therapy. More modern methods, specifically gas chromatographic-mass spectrometric, are more reliable in distinguishing these drugs (25). In acute poisoning cases, patient's blood drug concentrarion is more important than the urine levels. Blood levels are correlated with the patient's clinical conditions. Thus, immunoassay techniques such as FPIA, are preferred in emergency cases. These methods give rapid and sensitive results. The major disadvantages of immunoassay methods are their nonspecific nature and high costs. Although immunological tests are fast and sensitive, the specific results for involved drug or poison can only be obtained and confirmed by chromatographic methods, such as GC or GG/MS, as we presented in our study for three poisoned patients. Early admission to the emergengy departments of poisoned patients, proper biological sampling for analyses, and the comprehensive toxicological screening tests improves the quality of therapy.

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