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Editorial

Dear Readers,

We present to you the second issue of our journal for 2024. In this issue, we have published 2 original article, 1 review, 4 case reports and 1 erratum and that we think you will read with pleasure and interest. We hope that your scientific support will continue to increase in 2024. We would like to thank everyone who contributed to our journal for their support and contributions.

Best Regards.

Eurasian Journal of Toxicology Editorial Board

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Review

Eurasian Journal of Toxicology

Tricyclic Antidepressant Drug in Toxication

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Abstract

Tricyclic antidepressant (TCA) poisoning is one of the conditions that can lead to serious clinical consequences and require urgent medical attention. The clinical presentation of TCA toxicity can range from severe cardiotoxicity to mild antimuscarinic symptoms and signs. The most severe toxicity is to the cardiovascular, central nervous and peripheral nervous system. Sodium bicarbonate therapy is highly effective in treating arrhythmias and improving metabolic acidosis, although there is no known antidote for treatment. This review aims to present current information about the pathophysiology, clinical findings, diagnostic and therapeutic methods and prognosis of TCA poisoning.

Introduction

Tricyclic antidepressants are a class of drugs named after their structure with three benzene rings and are widely used in the treatment of various psychiatric conditions such as depression and anxiety disorders. Despite the many new drugs used in the treatment of depression, they are still the most commonly used group of antidepressant drugs after serotonin reuptake inhibitors (SSRIs)[1].

TCA's exert their antidepressant effects by inhibiting serotonin and noradrenaline reuptake. However, due to the narrow therapeutic index of these drugs, they carry a risk of serious toxicity at overdose of only a few times the therapeutic dose[2]. Therefore, TCA's are the main cause of morbidity and mortality in antidepressant-related poisonings.

Epidemiology

TCA poisonings are frequently encountered due to suicide attempts and accidental overdoses. In various studies, it has been reported that TCA poisoning is more common especially in young adults and middle age group. In addition, women have a higher risk of suicide attempt compared to men[3].

Pathogenesis

TCA's have a chemical structure consisting of a 7-membered central ring, 2 benzene rings on the outside and 3 aromatic rings including an aminopropyl region chain attached to the central ring4. TCA's may lead to serious complications due to their toxic effects on the central nervous and cardiac system. These drugs may cause cardiotoxicity by blocking Na+ channels, anticholinergic effects by inhibiting muscarinic receptors and seizures by antagonizing GABA-A receptors5. In addition, the effects of TCAs on K+ channels also play a role in the formation of cardiac arrhythmias. When TCA's are given at therapeutic doses, they are absorbed from the gastrointestinal system and reach their highest concentrations in plasma within 2-8 hours. In high

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dose intakes, decreased gastrointestinal motility due to their anticholinergic effects and ionization in acidic gastric fluids change their absorption kinetics and lead to delayed absorption. The oral bioavailability of TCA's is low and variable due to first pass elimination in the liver. This group of drugs is lipophilic. They are highly bound to tissues and plasma proteins, their virtual volume of distribution is large (15-40 L/kg) and their half-life varies between 7-58 hours depending on the drug[6,7]. Seventy percent of the total dose is excreted through the kidneys as inactive metabolites and the rest through bile[8].

Clinical Features

TCA's competitively suppress the action of acetylcholine at central and peripheral muscarinic receptors. This effect can be termed as anticholinergic effect. The main toxic effects of TCA's are on the central nervous system (CNS) and cardiovascular system. Cardiotoxic effects include hypertension and tachycardia, hypotension, cardiac conduction disorders and myocardial depression with membrane stabilizing effect9. With central antimuscarinic effect, they cause speech disorder, amnesia, ataxia, delusions, convulsion, delirium, agitation, confusion, sedation and coma, while with peripheral antimuscarinic effect, they cause fever, tachycardia, hypertension, dilated pupils, visual disturbance, urinary retention, dry skin, decreased oral and bronchial secretions, ileus, increased muscle tone and tremor [4,9].

Cardiovascular toxic effects are important for mortality in TCA poisoning. The cardiac effects of TCAs are caused by voltage-dependent Na+ and K+ channel blockade and postsynaptic inhibition of central and peripheral α-adrenergic receptors. Voltage-dependent Na+ channel blockade is the cause of arrhythmias, hypotension and conduction block caused by TCAs. Inhibition of fast Na+ channels in His-purkinje cells causes conduction abnormality[10]. Na+ channel blockade also results in hyponatremia, tachycardia, hypotension and acidosis. This effect is manifested on electrocardiography (ECG) as prolongation of PR and QRS and right axis deviation (RAD).

Severe sodium channel blockade causes hypotension, various heart blocks, RAD, QRS widening and ectopic heart beats as a result of negative inotropic effect. As a result of voltage-dependent K+ channel blockade, bradycardia and prolongation of QTc on ECG are observed[4]. QRS and QT prolongation seen on ECG is accepted as clinical evidence of cardiovascular toxicity[9,12]. Sinus tachycardia is a sensitive indicator of TCA intake, but it is not an indicator of whether a serious intoxication will develop[13].

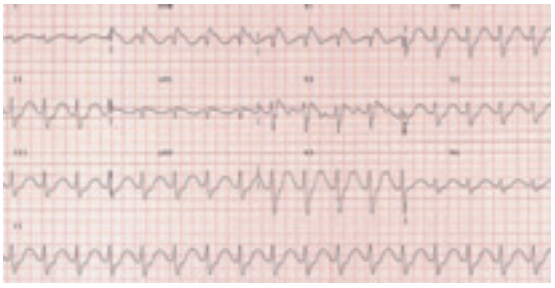

Figure 1: Cause of intoxication in the studied patients. MDT= Multiple Drug Toxicity.

Laboratory

Laboratory tests may reveal leukocytosis, hypopotassemia, hypocalcemia, hyperglycemia, and elevated liver function tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, lactate dehydrogenase, prothrombin time)[8]. Hypopotassemia may be observed at the time of initial presentation and may be secondary to sodium bicarbonate (NaHCO3) treatment.

If rhabdomyolysis develops due to recurrent seizures, elevated myoglobin, creatine kinase and potassium values may be found. Mixed type acidosis is most commonly seen in blood gas[14]. This is mostly due to elevated lactate levels as a result of respiratory depression and the hypotension that develops as a result of myocardial suppression causing tissue perfusion disorder[15].

Diagnosis

TCA intoxication should be considered in patients with QRS widening and QT prolongation accompanying findings such as lethargy, coma and seizure. Routine biochemical tests, ECG, blood gas measurement and chest radiography in patients with pulmonary edema are helpful in the diagnosis. The diagnosis of TCA intoxication is usually based on clinical findings. Electrocardiography (ECG) is one of the most important diagnostic tools; widened QRS complex and QT prolongation are typical. Sinus tachycardia is a sensitive indicator of TCA ingestion but is not an indicator of whether severe intoxication will develop4. Serum TCA levels can be measured but are not usually necessary for emergency treatment decisions.

Treatment

The aim of the initial evaluation is to identify life-threatening problems and initiate supportive treatment. Patients should first be evaluated for confusion, hemodynamic instability and respiratory failure. Then, intravenous access should be established, hydration should be started, cardiac monitoring and ECGs should be provided. A foley catheter should be inserted to prevent urinary retention and a nasogastric tube should be inserted if bowel sounds are absent. Patients who are initially asymptomatic may deteriorate rapidly in follow-up. Therefore, these patients should be followed very closely for the first few hours.

Activated charcoal treatment for gastrointestinal decontamination should be performed if the airway is protected and the patient is stable. Activated charcoal decontamination may be effective up to 2 hours after drug intake16. Since acidosis may increase cardiotoxicity and neurotoxicity, acidosis should be prevented. Seizures may occur after intoxication. Benzodiazepines can be used in the treatment of seizures, but anticonvulsants such as phenobarbital or propofol should be considered in resistant seizure cases. Sodium bicarbonate treatment should be given to hemodynamically unstable patients with seizures and patients with QRS prolongation[16]. Sodium bicarbonate treatment is given as 1 meq/kg intravenous bolus to narrow the QRS and maintain serum pH between 7.5-7.55, and then infusion treatment is started.

Intravenous fluid therapy should be started in hypotensive patients. Sodium bicarbonate treatment should be added to fluid treatment. However, if fluid and sodium bicarbonate treatment does not respond to hypotension, alpha-adrenergic agents should be started. If bradycardia does not respond to sodium bicarbonate, temporary pacemakers should be used. Antiarrhythmic drugs should be considered in acute TCA poisoning in cases not responding to sodium bicarbonate treatment. Class Ia (procainamide, quinidine, disopyramide) and class Ic (flecainide) are well-known sodium channel blockers and should not be used in acute TCA poisoning[13]. Intralipid emulsion treatment should be considered in hemodynamically unstable patients who receive an overdose of lipophilic TCAs. Dialysis and hemoperfusion are not effective in the treatment of TCA intoxication. Because TCAs are highly protein-bound and have a large volume of distribution and do not respond to dialysis[8].

Conclusion

Tricyclic antidepressant toxicity is an emergency situation with high mortality and morbidity. It should be managed and managed by a team consisting of an emergency physician, nurse, poison control specialist, cardiologist and neurologist. As in all poisoning cases, airway and respiratory stabilization should be provided first and circulation should be managed appropriately. Patients who are having seizures, hemodynamically unstable, and have QRS prolongation should be given sodium bicarbonate treatment. Temporary pacemaker treatment should be considered for patients with bradycardia. After interventions in the emergency department, hydration and close follow-up in the intensive care unit are recommended. The prognosis is generally good for patients treated in a timely manner. If a suicide attempt is suspected at the patient's discharge, a psychiatric consultation should be planned for the patient. Parents should be encouraged to keep all medications in a locked cabinet out of reach of children[17,18].

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Original Article

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Preclinical Benefit of Silymarin in Ketoconazole-Induced Hepatotoxicity

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Abstract

Background: Ketoconazole (KT) use has raised safety concern regarding hepatotoxicity. Silymarin (SL) is a natural bioactive substance with activities on a wide range of human pathologies. The protective activity of SL against KT-induced hepatotoxicity in rats was determined in this study.

Methods: Thirty adult Wistar rats of both sexes (220-300g) of n= 5/group were used. Groups I (Control) and II were orally administered with normal saline (0.2mL/day) and SL (200 mg/kg/day), respectively, whereas group III was orally administered with KT (200 mg/kg/day) for 28 days. Groups IV-VI were orally supplemented with SL (50 mg/kg/day, 100 mg/kg/day, and 200 mg/kg/day) before the administration of KT (200 mg/kg/day) for 28 days, respectively. On day 29, the rats were anesthetized and blood samples were collected and examined for biochemical markers. Liver tissues were collected and assessed for oxidative stress markers and histology.

Results: KT significantly ($p<0.01$) increased liver weight, and significantly ($p<0.001$) increased serum bilirubin, amino transferases, lactate dehydrogenase, gamma-glutamyl transferase, alkaline phosphatase, and liver malondialdehyde levels when compared to the control. KT significantly ($p<0.01$) decreased body weight, and significantly ($p<0.001$) decreased liver catalase, glutathione peroxidase, superoxide dismutase, and glutathione levels when compared to the control. KT caused hepatocellular necrosis. However, body, and liver weights and the aforementioned biochemical and oxidative stress markers were significantly restored in a dose-related fashion by SL supplementation at 50 mg/kg ($p<0.05$), 100 mg/kg ($p<0.01$), and 200 mg/kg ($p<0.001$) when compared to KT. The various doses of SL restored liver histology.

Conclusion: SL may have clinical benefit in KT-induced hepatotoxicity.

Keywords: Ketoconazole, hepatoprotection, silymarin, liver, toxicity, rats

Introduction

Drug-induced liver injury (DILI) was first described in the 1960s as a term that explains the spectrum of pathological responses by liver after been exposed to potentially hepatotoxic chemical substances.[1] DILI remains a significant and serious challenge in clinical practice and is still a diagnosis of exclusion. It is an infrequent occurrence with an incidence of 14–19 cases per 100,000 population, causing less than 1% of acute liver injury. Nevertheless, it is the most and known frequent cause of liver failure in the West, with a fatality rate of 10–50%.[2] DILI usually occurs when drug metabolism is altered causing hepatic damage attributed to factors including oxidative stress, inflammation, necrosis, apoptosis, and mitochondrial membrane damage.[3] Its manifestations ranges from liver enzyme elevations without any symptoms to liver failure, or death within days of it beginning. Effective drug treatment is scarce, but novel drugs are been explored.[4]

Ketoconazole (KT) has been used for more than four decades for the treatment of fungal infections. It is used as the prototype of human cytochrome P450 3A inhibitor in research involving drug interaction and metabolism during drug development.[5] In 2013, the European Medicines Committee on Medical Products for Human Use and the United States Food and Drug Administration collectively gave safety warnings and admonished decreased oral KT use because of potential risk of causing hepatic injury, drug interactions, and increased risk of adrenal insufficiency.[6] Incidence of 3.6-17.5% liver injury due to KT was documented in some clinical studies.[6,7] Preclinical studies have documented features of KT –induced hepatotoxicity which includes liver inflammation, oxidative stress, altered serum liver biochemical marker and liver architecture.[8,9] A number of factors have been speculated to be associated with KT-induced hepatotoxicity, which include immune mediated response, and oxidative stress.[10, 11]

Silymarin (SL) is an extract obtained from the dried fruits and seeds of the milk thistle plant (*S. marianum*). It is a complex combination of plant-derived chemical compounds known mostly as polyphenols, flavonolignans, and flavonoids (taxifolin, and quercetin) molecules.[12] The four dominant flavonolignan isomers in silymarin are silibinin, silichristin, isosilibinin, and silidianin, but silibinin

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(also called silybin) is the most prevalent and biologically active of the four isomers.[12] SL has a lot of biologic activities such as antioxidant, anti-inflammatory, and anti-fibrotic properties. Its antioxidant activity includes free radicals scavenging, production and enhancement of antioxidant activities,[13] while its anti-inflammatory action includes the inhibition of inflammasomes, and NF-kB activation.[14] Prior to modern and recent discoveries in medicine, it was recognized as an important and useful therapeutic treatment for numerous liver diseases in Asian and European traditional systems.[15] In preclinical studies, it has remarkably prevented liver dysfunction by restoring normal liver function and structure in paclitaxel[16] anti-tuberculosis drug[17] and paracetamol[18] induced hepatotoxicity. In the light of this information, this study examined whether SL can prevent KT-induced hepatotoxicity in rats.

Materials and Methods

Animals and drugs

KT and SL were supplied by Sigma Chemical Co., St. Louis, MO, USA. All other chemicals used were of analytical grades. The study was performed according to the procedure for the Care and Use of Laboratory Animals, 8th edition, 2011.[19] Thirty adult Wistar rats of both sexes weighing 220–300 g of aged 10–11 weeks sourced from the experimental animal unit of the Faculty of Pharmacy, Madonna University, Nigeria were used. The rats were randomly grouped into 6 of 5 rats/group, and kept under laboratory conditions (55 ± 5% relative humidity, 37 ± 3 °C temperature, and 12-h day and 12-h night cycle) for 14 days before the study began. SL[20] and modified doses of KT[8] were used.

Drug administration and sample collection

Group I, the control was administered with normal saline (0.2mL/day) whereas groups II and III were administered with SL (200 mg/kg/day) and KT (200 mg/kg/day), respectively for 28 days. Groups IV to VI were supplemented with SL (50, 100 and 200 mg/kg/day) prior to the administration of KT (200 mg/kg/day) for 28 days. On day 29, the experimental rats were anesthetized using ketamine (75 mg/kg/ip) and blood samples were collected via cardiac puncture in heparinised tubes and assessed for serum biochemical markers. Then, the liver tissues were removed and placed in a 10% formalin solution for histological analysis. Also, liver tissues were collected, washed in physiological saline and stored at −80 °C for oxidative stress marker assay.

Biochemical evaluations

Alkaline phosphatase (ALP), conjugated bilirubin (CB), alanine amino transferase (ALT), total bilirubin (TB), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and alanine amino transferase (AST) were evaluated using an auto analyser.

Determination of oxidative stress markers

Liver tissues were homogenized using 10% of 150 mM phosphate buffer (pH 7.4), with the aid of a homogenizer (IKA Overhead Stirrer, Staufen, Germany). The homogenates were centrifuged (Hettich Zentrifugen, Tuttlingen, Germany) at 12,000 rpm at 4°C for 10 min. The supernatants were decanted and assayed for oxidative stress markers. Glutathione peroxidase (GPX) and glutathione (GSH) were analysed using the processes described by Rotruck et al., 1973[21] and Sedlak and Lindsay, 1968,[22] respectively. Catalase (CAT) and Superoxide dismutase (SOD) activities were investigated as reported by Aebi, 1974[23] and Sun and Zigman, 1978[24] respectively. Malondialdehyde (MDA) was evaluated according to the protocol described by Buege and Aust, 1978.[25]

Histology of the liver

The collected liver tissues were passed through established histological procedures and were embedded in paraffin blocks. Sections of 4–6-µm-thick were prepared from the blocks using a microtome and stained with hematoxylin-eosin (H&E). Using a Leica DM500 microscope (Leica DFC295), the stained sections were examined and photographed.

Statistical analysis

This study used SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) for Windows Version 22 for data analysis. Two-ways analysis of variance (ANOVA) and Tukey's pair-wise multiple comparison tests were used for data analysis. The results were presented as mean ± standard error of mean (SEM). Significance was considered at $P < 0.05$; < 0.01; and < 0.001.

Results

Effects on body and liver weights

SL (200 mg/kg) did not produce significant ($p>0.05$) effects on the body and liver weights in comparison to control. In contrast, KT significantly ($p<0.01$) decreased body weight and significantly ($p<0.01$) increased liver weight in comparison to the control (Table 1). However, the altered body and liver weights were restored by SL supplementation at 50 mg/kg ($p<0.05$), 100 mg/kg ($p<0.01$), and 200 mg/kg ($p<0.01$) in comparison to KT (Table 1).

Table 1: Effects of silymarin on the body and liver weights of rats administered with ketoconazole.

Groups	Dose (mg/kg)	FBW (g)	ALW (g)	RLW(%)
I	Control	250.6± 14.8	4.18± 0.27	1.67±0.21
II	SL 200	256.2±16.3	4.23±0.13	1.65±0.18
III	KT 200	129.2±13.3*	8.22±0.18*	6.33±0.12*
IV	SL 50+ KT 200	177.3±15.7[a]	6.39±0.31[a]	3.60±0.09[a]
V	SL 100+ KT 200	228.6±14.4[b]	4.12±0.34[b]	1.79±0.20[b]
VI	SL 200+ KT 200	247.5±12.5[b]	4.05±0.35[b]	1.64±0.17[b]

Values are mean ± SEM, n = 5. S: NS: Normal saline, Silymarin, KT: Ketoconazole, *$p < 0.01$ when compared to control, [a]$p < 0.05$ and [b]$p < 0.01$ Differ significantly when compared to KT (ANOVA).

Table 2: Effect of silymarin on serum liver function markers of rats administered with ketoconazole

Groups	Dose (mg/kg)	AST (U/L)	ALT (U/L)	ALP (U/L)	TB (g/dL)	CB (g/dL)	LDH (U/L)	GGT (U/L)
I	Control	44.31±2.65	33.45±2.17	36.73±2.23	8.38±1.32	6.13±0.32	32.92±2.27	0.52±0.03
II	SL 200	41.94±4.79	32.71±3.08	37.24±6.65	8.18±0.57	5.82±0.68	32.53±5.12	0.58±0.07
III	KT 200	146.43±17.0*	132.55±12.3*	101.47±12.7*	20.37±3.07*	17.19±1.43*	126.72±14.3*	1.83±0.02*
IV	SL 50 + KT200	103.57±15.8[a]	83.62±14.2[a]	82.16±4.09[b]	16.24±2.16[a]	14.87±2.15[a]	70.14±5.14[a]	0.74±0.05[a]
VI	SL 100 + KT 200	74.46±7.07[b]	58.43±5.08[b]	61.44±3.53[c]	10.61±0.27[b]	10.21±0.64[b]	52.61±3.21[b]	0.65±0.04[b]
VI	SL 200 + KT 200	49.93±5.52[c]	37.92±4.16[c]	39.51±2.23[d]	8.81±0.39[c]	7.01±0.54[c]	35.81±2.42[c]	0.55±0.06[c]

Values are mean ± SEM, n = 5, SL: Silymarin, KT: Ketoconazole, AST: Aspartate aminotransferase, CB: Conjugated bilirubin, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, TB: Total bilirubin, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl tranferase,* $p < 0.001$ Differ significantly when compared to control. [a]$p < 0.05$; [b]$p < 0.01$ and [c]$p < 0.001$ Differ significantly when compared to KT (ANOVA).

Effect on serum liver biochemical markers

Serum ALT, ALP, AST, GGT, CB, LDH and TB levels remain unchanged ($p>0.05$) after SL (200 mg/kg) administration when compared to the control. But serum ALT, ALP, AST, CB, GGT, LDH and TB levels were significantly ($p<0.001$) elevated by KT when compared to the control (Table 2). Interestingly, serum ALT, ALP, AST, CB, GGT, LDH and TB levels were significantly restored in a dose-related fashion by SL supplementation at 50 mg/kg ($p<0.05$), 100 mg/kg ($p<0.01$), and 200 mg/kg ($p<0.001$) when compared to KT (Table 2).

Effect on liver oxidative stress markers

SL (200 mg/kg) administration had no significant ($p>0.05$) effects on liver GSH, SOD, CAT, GPX and MDA levels when compared to the control (Table 3). On the other hand, KT administration significantly ($p<0.001$) decreased liver GSH, SOD, CAT, and GPX and significantly ($p<0.001$) increased MDA levels when compared to the control (Table 3). But SL supplementation restored liver GSH, SOD, CAT, GPX and MDA levels in a dose-related fashion at 50 mg/kg ($p<0.05$), 100 mg/kg ($p<0.01$), and 200 mg/kg ($p<0.001$) when compared to KT (Table 3).

Effect on liver histology

Normal liver histology was observed in the control (Figure a) and SL (200 mg/kg) administered rats (Figure b). Hepatocellular necrosis was observed in the liver of KT administered rats (Figure c). More so, central vein congestion was observed in the liver of rats supplemented with SL (50 mg/kg) (Figure d), SL (100 mg/kg) (Figure e) and SL (200 mg/kg) (Figure f), respectively.

Discussion

The liver is a major organ which has array of functions. It metabolizes a wide range of drugs to water soluble compounds, which can be easily excreted.[26,27] Drug-induced hepatic injury is the most frequent reason known for the removal from the market of approved drugs, and it accounts for most cases of acute liver failure in the United States.[28,29] Despite the effectiveness of KT in treating fungal infections, the potential for endocrine dysregulation, and hepatotoxicity may undermine its benefits.[30] This study pre-clinically, examined the protective activity of SL against KT-induced hepatotoxicity. Administered SL had no deleterious impact on all evaluated indices in this study. Organ and body weights perturbation by drugs is imperative for toxicity assessment.[31] KT visibly decreased body and increased liver weights. This action may be a consequence of decreased body mass and liver inflammation. However, SL supplementation conspicuously restored body and liver weights. Biochemical markers are characteristic features, which can be objectively assessed and quantified as potential

Table 3: Effect of silymarin on liver oxidative stress markers of rats administered with ketoconazole

Groups	Dose (mg/kg)	SOD (u/mg protein)	CAT (u/mg protein)	GSH (µg/mg protein)	GPX (u/mg protein)	MDA (nmol/mg protein)
I	Control	45.74 ± 4.01	51.37± 6.01	38.67 ± 1.07	37.27 ± 3.41	0.18 ± 0.02
II	SL 200	47.07 ± 4.56	52.21 ± 5.03	39.16 ± 3.67	38.43 ± 1.39	0.17 ± 0.04
III	KT 200	19.85 ± 2.03*	20.31 ± 2.35*	11.21 ± 1.59*	11.27 ± 0.56*	0.92 ± 0.03*
IV	SL50 + KT 200	26.31 ± 3.12[a]	31.64 ± 3.07[a]	20.14 ± 0.43[a]	19.53 ± 0.76[a]	0.63 ± 0.09[a]
VI	SL 100 + KT 200	33.13 ± 4.12[b]	40.01 ± 5.31[b]	29.12 ± 2.78[b]	26.56 ± 2.58[b]	0.41 ± 0.06[b]
VI	SL 200 + KT 200	42.67± 4.01[c]	49.65± 6.61[c]	37.71 ± 3.54[c]	35.04 ± 3.18[c]	0.20 ± 0.03[c]

Values are mean ± SEM, n = 5, KT: Ketoconazole, SL: Silymarin, SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, MDA: Malondialdehyde, GPX: Glutathione peroxidase, * $p < 0.001$ Differ significantly when compared to control. [a]$p < 0.05$; [b]$p < 0.01$ and [c]$p < 0.001$ Differ significantly when compared to KT. (ANOVA).

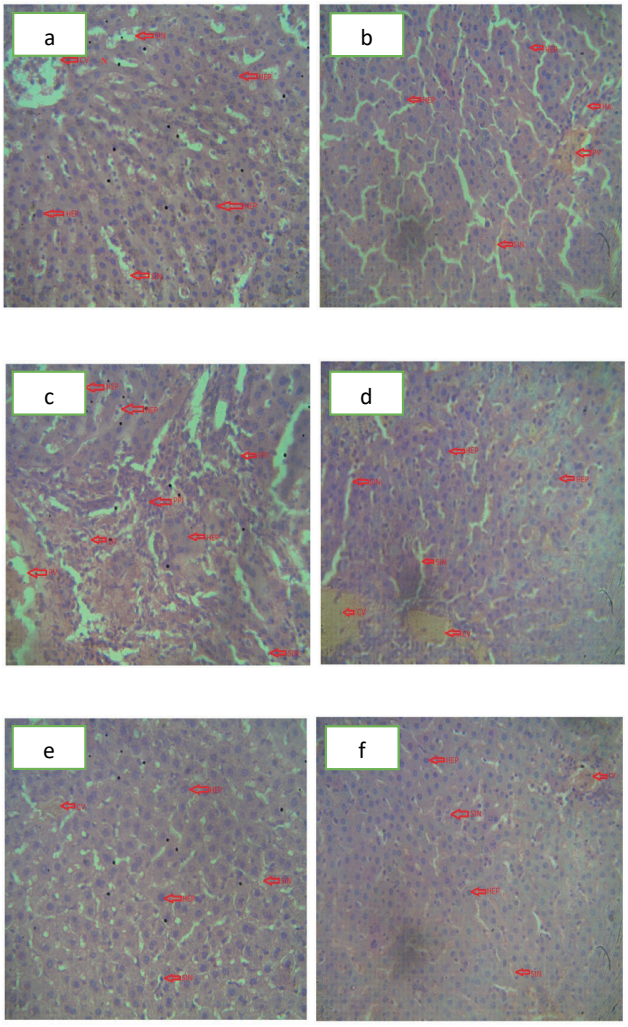

Figure 1: Liver histology of the control (Figure a) and SL (200 mg/kg) administered rats (Figure b). Liver of KT administered rats (Figure c). Liver histology of rats supplemented with SL; 50 mg/kg (Figure d), SL; 100 mg/kg (Figure e) and SL; 200 mg/kg (Figure f). HEP: Normal hepatocytes, CVN: Normal Central vein, PV: Portal vein, NEC: Necrosis, SIN; Sinusoids, HP: Hepatic artery, CV: Congested enteral vein.

indicators of any disease state or response to therapeutic regimen. Conventional indicators of liver function include AST, ALT, ALP, CB, GGT, LDH, and TB.[32,33] Altered levels of the aforementioned markers beyond the acceptable threshold especially in the presence of therapeutic agents is a pointer to an assault on the liver.[34,35] In this study, KT caused remarkable elevations in the serum levels of AST, ALT, ALP, CB, GGT, LDH, and TB. In agreement with our findings, Hamza et al., 2023[8] reported elevated levels of the aforementioned markers in adult rats administered with KT (100 mg/kg/day) for 5 days. Also, Rodriguez and Buckholz, reported similar findings in adult rats administered with KT (40 and 90 mg/kg/day).[36] The observed elevated levels of serum biochemical markers caused by KT may be related to the alterations of the permeability of the liver hepatocyte membrane causing the release of biochemical markers into the blood. In the current study, the assessment of the liver of KT administered rats showed altered liver architecture characterised by hepatocellular necrosis, which is similar to the findings reported by some scholars.[8] However, SL supplementation restored serum biochemical markers in a dose-related fashion. Also, various doses of SL restored liver histology.

Oxidative stress is the imbalance between the excess formation of reactive oxygen species and limited antioxidant defence. A direct consequence of excess reactive oxygen species production occurs due to its interaction with cellular biomolecules, such as proteins, DNA, and lipids causing structural alterations in the aforementioned biomolecules leading to cellular damage or death.[37] Oxidative stress has been considered as a primary conjoint pathological mechanism which detrimentally contributes to the initiation and progression of liver injury.[38] During liver injury, oxidative stress has been shown to cause notable depletions of liver antioxidant defence mechanism such as SOD, CAT, GPX and GSH. In the liver, SOD and CAT protect the cells from free radicals including superoxide radicals and hydrogen peroxide,[39] GSH, a thiols antioxidant detoxifies toxic compounds and heavy metals[39] whereas GPx reduces hydrogen peroxide and soluble lipid hydroperoxides.[40] The administration of KT caused oxidative stress marked by low liver levels of liver antioxidants (GSH, GPX, CAT and SOD). The observation is consistent with the induction of oxidative stress in the liver of adult rats administered with KT (100 mg/kg/day) for 5 days.[8] More so, in this study, KT caused elevation in the liver MDA level of rats. The observation indicates lipid peroxidation (LPO) caused by KT through the breakdown of liver poly unsaturated fatty acids which is consistent with previous findings.[8] LPO can disrupt membranes and produce reactive metabolites that can cause cellular dysfunction. LPO and its products can stimulate hepatic stellar cells and proinflammatory processes that can cause cell necrosis and apoptosis.[41] But this study found that SL supplementation inhibits KT-induced oxidative stress by restoring the liver levels of antioxidants and MDA in a dose-related manner. The observed hepatocellular necrosis caused by KT may be a consequence of KT-induced LPO, bimolecular damage and DNA fragmentation through oxidative stress. Despite the fact that the findings in this study showed that oxidative may be involved in KT-induced hepatotoxicity, immune-mediated mechanism was additionally suggested by some scholars.[8, 42]

In this study, perhaps SL prevented KT-induced hepatotoxicity by inhibiting oxidative stress. Studies showed that SL prevents oxidative stress by the inhibition of reactive oxygen species producing enzymes, scavenging of free radicals, antioxidant enzyme activation and the synthesis of protective molecules. Also, in drug/toxin-related hepatotoxicity, SL can protect against liver damage by preventing membrane permeability, chelation of intestinal ions and the inhibition of toxins at specific binding sites. This prevents the absorption and transportation of

harmful substances, especially in the hepatic phalloidin-transporting system.[14] Furthermore, the radical scavenging activity of SL can enhance hepatic lipid homeostasis by decreasing de novo lipogenesis through the down-regulation of acetyl-CoA carboxylase and peroxisome proliferator-activated receptor fatty acid synthase.[13] Due to the speculated involvement of immune mediated mechanism in KT associated hepatotoxicity as earlier mentioned, SL has immunomodulatory affects through the suppression of inflammasomes, TNF-α and the NF-κB signaling pathways.[14, 43]

Conclusion

SL inhibits KT-induced alterations in serum biochemical markers, liver oxidative stress markers and histology. This shows that SL may have clinical benefit against KT-related hepatotoxicity.

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Original Article
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Experiences Of Emergency Physicians On Scorpion Stings

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Abstract

Every year, the United States records about 200 cases of botulism. Those who inject substances such as heroin, use homemade alcohol, and eat improperly prepared canned food are at risk of contracting this extremely rare disease. As seen in this case, those treated with Clostridium Botulinum Toxin are also considered to be in the risk group. However, iatrogenic botulism cases are much rare; and in the literature, case reports of botulism after intragastric Clostridium Botulinum Toxin administration are rare. We aimed to present these cases to draw attention to this rare condition in patients who presented to the emergency department with complaints such as weakness, dyspnea, and diarrhea.

Keywords: Stomach, Botox, Adverse effects, Iatrogenic disease

Introduction

Scorpion envenomation is an important public health problem, especially in tropical and subtropical regions, due to the severe clinical symptoms and serious complications, including death[1]. Although venomous scorpions show a wide geographical distribution, almost all species harmful to humans belong to the Buthidae family[2].

In Turkey, scorpion envenomation is particularly common in the southeastern region due to geographical location, climate, and socioeconomic structure. The most prominent scorpion species found in Turkey are Androctonuscrassicauda, Leiurusquinquestriatus, Mesobuthuseupeus, and Mesobuthusgibbosus species of the Buthidae family[3].

In scorpion stings, clinical manifestations are divided into local (pain affecting the involved dermatome, local edema, localized paresthesia, and pruritus) and systemic (tachycardia, tachypnea, respiratory distress, shock, agitation, and altered state of consciousness, etc.). Most victims of stings do not develop envenomation, and systemic symptoms are rare. Localized symptoms occur in 97% of affected people. Pain is the most common localized reaction. The most feared complications are associated with cardiac involvement. Cardiogenic shock and pulmonary edema are responsible for deaths in the first hours. Children under 5 years of age are the most at risk group[3-5].

Patients are classified into four classes according to the severity of clinical symptoms; Class I is local only, Class II is minor systemic, Class III is major systemic, and Class IV is fatal. The severity of symptoms is influenced by many variables related to the scorpion (type and size of the scorpion, type of toxin), the exposure (number of stings, anatomical location of the sting, amount of venom injected, time until treatment administration) and the patient (age, weight, comorbid diseases, etc.)[6].

The general approach to bites and stings includes wound care, tetanus prophylaxis, and symptomatic supportive care. In scorpion sting cases, antivenom should be administered in the presence of appropriate systemic and local indications[7].

In Turkey, especially in Diyarbakır, Şanlıurfa, and Mardin provinces, a horse-derived antivenom is produced using venom and antivenomes obtained from

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Androcutanuscrassicauda scorpions, a species that causes life-threatening sting cases. This antivenom also has protection against many scorpion venoms at different rates. Studies conducted in our country have shown that the antivenom produced from A. crassicauda yields better results than the best-known antivenoms[8].

In our country, horse-derived scorpion antivenom is available in several commercial forms with different routes of administration [intravenous (IV), subcutaneous (SC), or intramuscular (IM)][9-10]. The dose to be used does not depend on the age or body weight of the patient; it is determined by the physician according to the clinical situation and repeated if necessary. Some side effects may occur during antivenom administration. It is recommended to take precautions before and during administration for acute side effects.

Correct and effective intervention in the emergency department for patients exposed to scorpion stings, rapid indication of scorpion antivenom, and management of side effects are life-saving. The aim of this study is to contribute to the literature by investigating the knowledge and skills of emergency physicians about scorpion stings, the problems experienced in the management of these patients, and whether physicians comply with current guidelines in patient management.

Methods

This survey was conducted with physicians working in the emergency department via e-mail. A questionnaire form created by the researchers was used as a data collection tool. In the questionnaire form, in addition to questions about demographic information, a total of 16 questions were asked to measure the participants' experiences about scorpion sting cases and scorpion antivenoms. Ethical approval was obtained from the local ethics committee for the study (KAEK-2016/81).

IBM SPSS Statistics for Windows, Version21.0 (IBM Corp. Armonk, NY: USA. Released 2012) package program was used for statistical analyses. For descriptive statistics, categorical variables were shown as number of cases and (%). Chi-square and Fisher's exact tests were used to analyze the relationship between categorical variables. $p<0.05$ was considered statistically significant. Results were given in a 95% confidence interval.

Result

Of the 282 physicians who participated in our study, 53.9% (n=152) were female and 46.1% were male. According to the title, 45.7% (n=129) of the participants were emergency medicine physicians and 45.0% (n=127) had 5-9 years of experience in emergency medicine. When the distribution according to geographic regions was analyzed, the highest number of participants was from the Aegean Region with 25.5% (n=72) and the lowest was from the Mediterranean Region with 5.3% (n=15). The analysis of the demographic data of the participants is given in Table 1.

Table 1: Demographic data of emergency physicians

		N	%
Age	34 and below	165	58,5
	35 to 44	96	34,0
	45 and above	21	7,4
Gender	Female	152	53,9
	Male	130	46,1
Title	General Practitioner	82	29,1
	Emergency Medicine Assistant	71	25,2
	Emergency Medicine Specialist	129	45,7
Working Time in the Emergency Department	Less than 5 years	108	38,3
	5-9 years	127	45,0
	10-14 years	24	8,5
	15-19 years	23	8,2
Employed Institution	State Hospital	108	38,3
	Education Research Hospital	90	31,9
	University Hospital	84	29,8
Geographic Region	Marmara Region	57	20,2
	Aegean	72	25,5
	Mediterranean	15	5,3
	Central Anatolia	26	9,2
	Eastern Anatolia	34	12,1
	Southeastern Anatolia	51	18,1
	Black Sea	27	9,6

The proportion of physicians who regularly checked the availability of scorpion antivenom in the emergency department was 31.6% (n=89). Among all title groups, emergency medicine specialists had the highest rate, while emergency medicine assistants had the lowest rate, which was statistically significant (p=0.01) (Table 2).

To make antivenom decisions, general practitioners need consultation significantly more than emergency medicine specialists (p=0.01).

Our study revealed that only 25.5% (n=72) of emergency physicians practiced pre-antivenom skin testing. No significant difference was found between title groups (p=0.67).

For the necessary intervention for complications that may arise during the administration of scorpion antivenom, 73% (n=206) of the participants took the necessary precautions before administration. This rate increases to 80.6% (n=104) in Emergency Medicine specialists, which is statistically significantly higher than the other groups (p=0.04). No significant difference was found when analyzed institutionally or regionally.

Administration of antivenom via IV route was significantly more preferred by emergency medicine specialists compared to other groups (p=0.01). (p=0.01) 31.7% of general practitioners (n=26) administered antivenom as "half to the wound edge/half IM". This rate is also statistically significantly higher in other groups (p=0.01).

Tetanus prophylaxis was administered to patients with scorpion stings by 269 (95.4%) of the participating

Table 2: Practice experiences according to title groups

		Titles			
		General Practitioners n (%)	**Emergency Medicine Assistants n (%)**	**Emergency Medicine Specialists n (%)**	**P**
Regular Control of Antivenom	Yes	25 (30,5)	6 (8,5)	58 (45,0)	0,01
	No	57 (69,5)	65 (91,5)	71 (55,0)	
Requesting Consultation for Antivenom Decision	Yes	57 (69,5)*	22 (31,0)	11 (8,5)	0,01
	No	25 (30,5)	49 (69,0)	118 (91,5)*	
Skin Test before Antivenom Administration	Yes	20 (24,4)	16 (22,5)	36 (27,9)	0,67
	No	62 (75,6)	55 (77,5)	93 (72,1)	
Taking Precautions for Complications	Yes	54 (65,9)	48 (67,6)	104 (80,6)*	0,03
	No	28 (34,1)	23 (32,4)	25 (19,4)	
Antivenom Route of Administration	IV	38 (46,3)	34 (47,9)	91 (70,5)*	0,01
	İM	10 (9,3)	7 (9,9)	15 (11,6)	
	SC	8 (9,8)	7(9,9)	15 (11,6)	
	WE	0 (0)	0 (0)	0(0)	
	HWE/HIM	26 (31,7)*	19 (26,8)	11 (8,5)	
	Other	0(0)	0(0)	0(0)	
Tetanus Prophylaxis	Yes	75 (91,5)	68 (67,7)	126 (97,7)	0,10
	No	7 (8,5)	3 (4,2)	13 (2,3)	
Antibiotic Prophylaxis	Yes	52 (63,4)*	42 (59,2)	52 (40,3)	0,02
	No	30 (36,6)	29 (40,8)	77 (62,2)*	
Service Hospitalization Problem	Yes	42 (51,2)	46 (64,8)	77 (59,7)	0,22
	No	40 (48,8)	25 (35,2)	52 (40,3)	

IV: Intravenously, IM: Intramuscular, SC: Subcutaneous, WE: Woundedge HWE/ HIM: Halfwoundedge / Halfintramuscular *Post Hoc analyses were applied for the groups.

physicians. No significant difference was found between title groups.

To the question "Do you administer antibiotic prophylaxis?" 51.8% (n=146) of all participating physicians answered "yes". This rate was statistically significantly higher in general practitioners while it was significantly lower in emergency medicine specialists (p=0.02).

The rate of emergency physicians who stated that they experienced problems in the service hospitalizations of patients with an indication for hospitalization due to scorpion sting was 58.5% (n=165). Although this situation did not create a significant difference between title groups, emergency physicians working in university hospitals were statistically significantly the group with the highest number of hospitalization problems (p=0.01).

Patient death due to scorpion sting was experienced by 4.3% (n=12) of the emergency physicians surveyed. The distribution of these cases according to geographical regions was as follows: 41.7% (n=5) in the Southeastern Anatolia Region, 25% (n=3) in the Eastern Anatolia Region, 16.7% (n=2) in the Marmara Region, and 16.7% (n=2) in the Aegean Region.

Discussion

Most cases of scorpion sting have minor local signs and therefore usually require only wound care, analgesics, and tetanus prophylaxis. Patients should be kept under observation for 4 hours. The onset of life-threatening systemic symptoms is quite rapid, on average 14 minutes. In children, it can be much faster. These patients should be prepared for endotracheal intubation because of the possibility of rapid onset of severe pulmonary edema. In indicated patients, antivenom given within 4 hours of the sting may reduce the duration and severity of clinical symptoms[7-11].

The key to minimizing preventable deaths in sting cases is to ensure timely access to treatment. The availability and accessibility of antivenom should be checked regularly[12]. Our study showed that only 31.6% of emergency physicians checked the availability of antivenom in their institutions. Although we could not find a literature study to compare this result, this low rate may be a result of the distribution of duties within the institution or the low frequency of encountering sting cases.

In scorpion antivenoms, although undesirable protein and albumin fractions have been reduced with the new F(ab')2 products, as with all antivenoms of animal origin, both acute and delayed allergic reactions, including serum sickness, may develop[13-14].

The spectrum ranges from common side effects such as pain/swelling/redness at the injection site, skin rash, itching, and urticaria to life-threatening side effects such as anaphylactic shock or serum sickness. The onset of serum sickness may occur 6-10 days after administration[9].

Intubation equipment, epinephrine, and IV fluids should be available before the administration of antivenom as a precaution against anaphylactic shock[11].

Intradermal skin testing is recommended before scorpion antivenom. In positivepatients, antivenom can be administered after the patient is observed for at least 1 hour after IV antihistamine and adrenaline infusion before antivenom[15].

Our study shows that only 25.5% (n=72) of the participating emergency physicians performed skin testing. Although a negative skin test does not exclude the possibility of complications related to antivenom, the possibility of complications can be reduced with premedication, especially in atopic individuals. The rate of physicians who prepared for possible complications was 73% (n=206) in our study. Emergency medicine specialists were significantly more cautious in this regard. It is noteworthy that emergency physicians showed high sensitivity in taking precautions against the development of complications, but largely ignored the skin test. This result may be due to the desire to administer the antivenom as soon as possible and/or the fact that a negative skin test does not exclude the possibility of complications.

When the literature is reviewed, it is seen that scorpion antivenom is usually administered by IV route11,16. In the package inserts of antivenoms available in our country, it is reported that some commercial forms can be administered by IV, IM, or SC routes. Our study revealed that emergency medicine specialists preferred the IV route at a significantly higher rate than other groups. Another interesting result was that 19.9% (n=56) of the physicians adopted the "half to the wound site/half IM" method of administration, although no supporting recommendation was found in the literature review and package insert information. In general practitioners, this rate was 31.7% (n=26) and significantly higher than the other groups. This method of administration is only recommended when the risk of developing compartment syndrome in the injured extremity during the administration of rabies immunoglobulin is anticipated due to the amount of fluid to be applied around the wound[17]. This result showed us that almost one-third of general practitioners were confused in the management of environmental emergencies.

Tetanus prophylaxis is routinely recommended in the management of scorpion stings[2,10,11]. Our study results showed that almost all physicians followed this recommendation. Prophylactic antibiotic administration is not recommended because the risk of local superinfection is not very high, and wound cleansing and antisepsis are sufficient[18]. However, our results show that more than half of the physicians recommend antibiotic prophylaxis for sting patients. This rate is significantly higher especially in general practitioners compared to other physicians.

Our study revealed that scorpion sting patients with an indication for hospitalization had problems in service hospitalization. The rate of physicians who stated that they had problems in this regard was 58.5% (n=165). The problem of service hospitalization was significantly higher in university hospitals compared to other institutions. In the literature, a similar result was found in snake bites in our country[19]. This result suggests that there is a lack of organization in university hospitals in patients who are treated in the emergency department due to environmental emergencies such as bites and stings and who require follow-up.

Conclusions

Our study investigated the knowledge and skills of emergency physicians regarding scorpion stings, whether they comply with current guidelines, and the problems experienced in patient management.

When our results are considered; in-professional training on the management of environmental emergencies should be planned and regulations should be made especially in undergraduate education.

There is a need for more detailed studies to reveal the causes of the problems related to the management of these patients after the emergency department and concrete steps to solve these problems.

Limitations

In our study, we tried to keep the number of questions limited due to concerns about the participation rate; therefore, the subject could only be presented in outline. This prevented us from analyzing the causes of some of the problems and focused only on the existence of the problem.

The number of participants was limited. Therefore, there was not a homogeneous distribution at regional, institutional, and title level.

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Case Report

Eurasian Journal of Toxicology

A Case of Forgotten Poisoning in a Patient Presenting with Speech Disorder

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Abstract

Anticholinergic poisoning is one of the most common causes of poisoning in the emergency department. Beautiful hawthorn (atropa belladonna), which is found in our country, is one of the plants that can cause anticholinergic syndrome. It is important in the differential diagnosis in cases progressing with general status disorder and loss of consciousness and psychotic findings. The onset of anticholinergic intoxication varies depending on the toxin and occurs within one to two hours following oral ingestion. The diagnosis of anticholinergic poisoning is based on clinical findings. Anticholinergic poisoning is easily diagnosed when a history of exposure to an anticholinergic substance is obtained and the patient shows altered mental status, delirium or hallucinations. However, in cases with no history and unknown exposure, the diagnosis of anticholinergic intoxication is considered when clinical signs and symptoms caused by mental status disorder and anticholinergic effects are detected on physical examination.

A 75-year-old woman was admitted to the emergency department with complaints of slurred speech, altered consciousness and facial shifting that started about 2 hours ago. On physical examination, the patient was incoopere and disoriented, GCS:12 eyes were spontaneously open, obeying orders but making unintelligible sounds, nuchal rigidity was suspiciously positive, bilateral babinski reflex was positive. On admission vital signs were blood pressure 144/72 mmHg, pulse 98/min, temperature 37 °C, SO2 94%, fingerstick blood glucose 104 mg/dl and ECG was in normal sinus rhythm. There were no acute pathologic findings on both brain CT and brain MR imaging. In the control physical examination, both pupils were mydriatic, IR -/- and the patient had dry mouth. According to the anamnesis obtained from another relative of the patient, it was learned that they ate spinach in the evening and speech disorder started afterwards. The patient was diagnosed with anticholinergic intoxication considering that the spinach eaten by the patient with clinical findings might have been mixed with the beautiful hawthorn weed.

In this case report, we aimed to emphasize the importance of detailing the anamnesis and the necessity of a complete systemic examination in patients presenting with confusion and speech disorder.

Keywords: Atropa belladonna, Poisoning, Emergency service

Introduction

Anticholinergic intoxication is one of the causes of intoxication in the emergency department. They may present with symptoms including general status disorder, altered consciousness, confusion, mydriasis, dry and hot skin, urinary retention, tachycardia, decreased and complete disappearance of bowel sounds[1,2]. The diagnosis of anticholinergic intoxication is based on clinical findings. Anticholinergic intoxication can be easily diagnosed when a history showing exposure to an anticholinergic substance is obtained and the patient shows mental status change, delirium or hallucinations; however, in cases with no history and unknown exposure, the diagnosis of anticholinergic intoxication is considered when mental status disorder and clinical signs and symptoms are detected on physical examination[3]. Gastric lavage, activated charcoal, NaHCO3, supportive symptomatic treatment and physostigmine are administered in patients presenting within the first 1 hour.

With this case report, we aimed to draw attention to beautiful hawthorn intoxication which has become a classic in textbooks but is not in the first place among the preliminary diagnoses in the clinic.

Case Presentation

A 75-year-old woman was admitted to the emergency department with complaints of slurred speech, altered consciousness and facial shifting that started about 2 hours ago. According to the anamnesis taken from the patient's relatives, it was learned that she had spoken normally with her son about 5 hours before admission but could not speak with her daughter about 2 hours ago. According to the anamnesis taken from the relatives, the patient did not have any loss of sensory power. The patient had a known history of diabetes, hypertension and colon cancer. He was operated 4.5 years ago for colon cancer. On physical examination, the patient was incoopere and disoriented, GCS:12, obeyed commands but made unintelligible sounds, pupil and light reflexes examination were normal, nuchal rigidity was suspiciously positive, bilateral babinski reflex was positive. On admission vital values were blood pressure 144/72 mmHg, pulse 98/min, temperature 37 °C, SO2 94%, fingerstick blood glucose 104 mg/dl and ECG was in normal sinus rhythm. Due to the sudden onset of speech disorder, the

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patient underwent brain CT scan for central pathology, but there was no acute pathologic finding. There were findings of atrophy and periventricular leukomalacia. Laboratory parameters were pH:7.44, pCO2:41, HCO3:27.4, lactate:1.5, WBC:7.54, Hb:11.2, plt:238, BUN:23, cre:0.95, GFR:59, AST:16, ALT:13, Na:138, K:4.5, Cl:103, CRP:4.9, INR:1. Brain MRI was ordered with a prediagnosis of acute ischemic LVH, but there were no acute pathologic findings on MRI. Although brain CT and brain MRI examinations wew normal, a clinical evaluation was requested from the neurology consultant and neurology consultant stated that she did not think of a structural neurological pathology in the patient. Urgent neurologic treatment was not recommended. When structural pathologies of the brain are excluded, anamnesis was deepened with a control physical examination. In the control physical examination, both pupils were mydriatic, IR -/- and the patient had dry mouth. According to the anamnesis obtained from another relative of the patient, it was learned that they ate spinach in the evening and speech disorder started afterwards. It was thought that the spinach eaten by the patient with clinical findings might have been mixed with the beautiful hawthorn weed and anticholinergic intoxication was considered and the patient was consulted with the anesthesia clinic and transferred to the intensive care unit. The patient was symptomatically followed up for 3 days in the intensive care unit and was discharged with complete recovery.

Discussion

With the increase in the consumption of some green leafy plants in the winter season in our country, it causes us to encounter various intoxications as a result of the consumption of some plants mixed among these plants without being cleaned. One of these mixed plants is Atropa Belladonna (beautiful heliotrope). Its fruits and leaves contain high levels of atropine, scopolamine and hyoscyamine alkaloids. When consumed, the alkaloids in this plant block postganglionic muscarinic receptors and muscarinic receptors in the central nervous system, resulting in anticholinergic intoxication. Anticholinergic intoxication is characterized by peripheral effects in addition to changes in consciousness, hallucinations and loss of recent memory as a result of central effects. Among these effects, mydriasis, dryness in mucous membranes, high fever, tachycardia, dry skin, ileus and urinary retention are among the causes4. In patients presenting with altered consciousness, fingertip blood glucose should be checked to exclude the diagnosis of hypoglycemia leading to altered consciousness5. In the initial evaluation of our patient, fingertip blood glucose was checked. Patients usually present with symptoms that occur within one to two hours following oral ingestion. In our patient, he presented to us with symptoms occurring approximately two hours after ingestion of food. The diagnosis of the patient is made on the basis of clinical signs and symptoms caused by antimuscarinic effects6. Since our patient had complaints of altered consciousness and facial asymmetry, we first performed brain CT and brain MRI to rule out central pathology. Since there were no pathological findings in radiological examinations, we diagnosed anticholinergic intoxication based on detailed anamnesis and physical examination. Anticholinergic intoxications are related with drugs and substances that prevent the binding of acetylcholine to muscarinic receptors. Therefore, the use of such drugs should be questioned in the patient's medical history for differential diagnosis. Antihistamines (diphenhydramine, hydroxyzine, promethazine), antiparkinsonian drugs (benztropine, trihexyphenidyl), antipsychotics (phenothiazines, butyrophenones), belladonna alkaloids and their analogues (atropine hyocyanin, ipratropium), mydriatics (cyclopentolate, tropicamide)7. Most patients respond well to supportive treatment in anticholinergic intoxications. Some patients who do not respond may require the use of physostigmine as antidote treatment. Physostigmine inhibits anticholinesterase reversibly by crossing the blood brain barrier8. Our patient responded to symptomatic supportive treatment and was discharged.

Conclusion

Considering the importance of a detailed anamnesis in patients with symptoms of anticholinergic toxic syndrome, detailed questions should be asked about vegetable consumption and medications used, especially in winter months. This may guide the differential diagnosis. Furthermore, intensive care follow-up is necessary for closer monitoring of central and peripheral clinical effects that may occur during anticholinergic poisoning.

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Case Report

Eurasian Journal of Toxicology

Two Case of Botulism Developed After Endoscopic Clostridium Botulinum Toxin Administration to the Stomach Wall

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Abstract

Every year, the United States records about 200 cases of botulism. Those who inject substances such as heroin, use homemade alcohol, and eat improperly prepared canned food are at risk of contracting this extremely rare disease. As seen in this case, those treated with Clostridium Botulinum Toxin are also considered to be in the risk group. However, iatrogenic botulism cases are much rare; and in the literature, case reports of botulism after intragastric Clostridium Botulinum Toxin administration are rare. We aimed to present these cases to draw attention to this rare condition in patients who presented to the emergency department with complaints such as weakness, dyspnea, and diarrhea.

Keywords: Stomach, Botox, Adverse effects, Iatrogenic disease

Introduction

Botulism, while uncommon, is a disease that should be considered due to its serious consequences[1]. While there have been eight identified forms of Clostridium Botulinum Toxin (CBT), the pathogen responsible for the disease, only types A, B, and E (rarely types H, G, and F) have been found to cause illness in humans[2, 3].

Botulinum toxin induces muscle weakness and flaccid paralysis in the nervous system by irreversibly altering neuromuscular junction sites and the presynaptic release of acetylcholine. If not treated promptly, mortality due to respiratory muscle involvement ranges from 5% to 10%. The purified and diluted form of "Neurotoxin A" is used in clinical and cosmetic applications[4, 5].

In the treatment of obesity, many methods, including surgical procedures, are being tried. As one of them CBT injected into the stomach wall is applied to delay gastric emptying by reducing gastric motility6-8. We discovered iatrogenic botulism in two of our cases after using CBT for obesity treatment, and we wanted to share these cases to raise awareness of this rare condition among patients seeking care at the emergency department. Informed consent was obtained from the patients.

Case 1

CBT was administered to the stomach of a 40-year-old male patient in order to help him lose weight. His body mass index (BMI) was determined to be 41, and he traveled from another county specifically for this treatment as he did not benefit from other obesity treatments. The treatment concluded with an endoscopic injection of 1500 units of a solution containing 500 units of Clostridium Botulinum type A toxin-hemagglutinin complex into the antrum and pylorus regions of the stomach. Week following the procedure, he had complaints of muscle soreness and weakness that gradually increased, as well as other symptoms such as blurred and double vision, difficulty speaking, and shortness of breath. When he applied to our hospital, it was found that approximately 20 days had passed since the procedure, and he had diarrhea, persistent weakness, and dizziness, as well as trouble speaking and shortness of breath. It was observed that his temperature (T) was 36.7 °C and blood pressure (BP) was 140/80 mmHg. The sPO2 value was in the range of 90-93.

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Case 2

On the same day, a 37-year-old female patient with a BMI of 37, the spouse of the first patient, underwent gastric CBT. The patient was admitted to our hospital with her spouse after a week of muscle soreness, dizziness, double vision, and new-onset shortness of breath as a result of the procedure. Upon admission, the most common symptoms were dizziness and impaired vision, with swallowing difficulties persisting despite a decrease in severity. Also, family reported that the patient's tone of voice had changed. The systemic examination was normal. The vital signs of the patient were: T:36.6°C, BP:130/70 mmHg, BG:135mg/dL and SpO2:96.

Two patients were admitted to the Toxicology Intensive Care Unit for treatment and follow-up. Regression of the patients' symptoms was observed after strict monitoring with Pyridostigmine 60 mg 3 times daily, supported by symptomatic treatment. Among the patients who were hospitalized and began treatment on the same day, the female patient's symptoms, which were mild, improved rapidly after the first few days. The male patient's symptoms, which were more severe, decreased significantly after the fifth day. Two patients who had no complaints other than fatigue and had normal vital signs were discharged with recommendations after one week of treatment. During the follow-up, it was discovered that the female patient's complaints had been fully resolved, whereas the male patient's complaints of weakness and malaise persisted for another month.

Discussion

Cases of iatrogenic botulism are very rare, and no case reports involving the administration of gastric CBT have been found in the literature, except for patients who received similar treatment during the same time period as our cases. As seen in our case, those treated with CBT are considered to be in the risky group in terms of botulism[3, 9].

Reports suggest that other factors such as the injection technique that was used, the needle size and angle, the injection speed, and the volume of the injected substance influence the toxicity of botulinum[10-12]. There are also studies reporting that commercial CBT preparations differ in potency. It is known that 1500 units of Clostridium botulinum type A toxin were administered in our cases. There are reports in the literature stating that 500 units were administered with no toxic effects observed. On the other hand, the literature places an emphasis on how little research there is that is related to the maximum dosage[11, 13]. Further research is needed on this subject.

The diagnosis is primarily dependent on clinical and anamnesis findings (Table 1). Indicators of iatrogenic botulism include the presence of symptoms quickly after a procedure, the use of an unregistered product, and the production of the procedure in an unsuitable business setting. The main approach for these patients is antitoxin and supportive treatment. Early botulism antitoxin administration (within the first 48-96 hours) will result in rapid clinical improvement. Studies have shown that treatment with Pyridostigmine may also be beneficial in cases where the antitoxin cannot be obtained or in delayed cases3, [14-17].

Table 1: Clinical Symptoms Raising Suspicion of Botulism[15]

Absence of Fever (<37.8 °C)[1]
At least one of the following symptoms
Blurred vision
Diplopia
Impaired speech[2]
Hoarseness or change in tone of voice
Dysphagia, accumulation of secretions in the mouth
Thick Tongue
At least one of the following symptoms
Ptosis
Fatigue in the extraocular eye muscles (decreased tracking of objects)
Facial paralysis, change in facial expression
Fixed pupils[3]
Descending paralysis, Cranial nerve palsies

[1]Patients may have fever due to a secondary infection [2]Consciousness is expected to be intact in patients [3]Slow pupil movements are not considered as fixed pupils.

Conclusion

Given the insufficiency of normal laboratory testing in the emergency department and in many other facilities for early diagnosis, it is critical to inquire about this situation in the anamnesis of the patients and to consider the possibility of botulism. In addition, due to their increased use in recent years, it is necessary to take crucial steps to ensure the reliability of CBT preparations and the expertise of their practitioners.

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Case Report

Eurasian Journal of Toxicology

Acute Renal Failure as a Result of Mushroom Poisoning

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Abstract

Mushroom poisonings may present with early findings in the first 2 hours and late findings between 6 hours and 20 days. In this article, it was aimed to emphasize that mushroom poisoning should be considered in the differential diagnosis of renal failure and coma, as in the patient whose history was learned to have eaten mushrooms 10 days ago.

Keywords: Acute Renal Failure, Mushroom Poisoning, Hemodialysis

Introduction

Mushroom poisonings may present with early findings in the first 2 hours and late findings between 6 hours and 20 days. Renal failure can be seen in the acute period in fungi containing orellin and allenic norleucine, and within 2-6 days in species containing cyclopeptide[1]. Patients apply with complaints of nausea, vomiting, diarrhea, unconsciousness in the first 3 days after ingestion of mushrooms containing nephrotoxin, and oliguria and anuria within 3-20 days. Patients may need dialysis in addition to supportive treatment[2].

Case

Twenty-nine-year-old male patient was brought to the emergency room due to deterioration in his general condition and unconsciousness. In the patient's history, there were nausea and vomiting after eating mushrooms about 10 days ago, and antibiotic initiation in an external center. The mushroom was eaten 10 days ago and no treatment other than antibiotics was given. On physical examination, the general condition was poor, unconscious, and Glasgow coma scale was 7. The patient who had sudden cardiac arrest in the emergency department was admitted to the intensive care unit after resuscitation. The patient's blood pressure was 130/90 mmHg, pulse: 112/min, fever: 36.5 C, respiration: 36/min. Other physical examination revealed no abnormality. In the laboratory tests of the patient: Hemoglobin 12.5 g/dL(12,2 -18,1), platelet 34610^3/µL(142 - 424), glucose 89 mg/dL(74 - 109), Urea 189 mg/dl(17 -43), Creatinine 14 mg/dL(0,5 - 1,2), sodium 127mmol/L(136 - 146), potassium 7.5 mmol/L(3,5 - 5.1), Aspartat Aminotransferaz 47 U/L(0 - 40), alanin Aminotransferaz 13 U/L(0 - 41), Calcium 8.3 mg/dL(8,6 - 10,2), Troponin I 2.39ng/ml, amylase 146U/L, kreatin kinaz 1279IU/L., kreatin kinaz -MB 121I U/L., Gama glutamil transferaz 11 U/L(12 -64), Lipase 35U/L and metabolic acidosis(pH=7.20) was detected in blood gas. The patient was taken to emergency hemodialysis. Hemodialysis was applied for 3 days. Control blood values normal. On the 7th day, the patient was extubated. On the 10th day, the patient recovered completely and was discharged voluntarily.

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1a 1b

Photo 1a: Cultivated mushrooms (Taken from the archive of Prof. Dr. Ali Karakuş)
1b. Natural mushrooms(Taken from the archive of Prof. Dr. Ali Karakuş)

Discussion

Mushroom poisonings constitute 1.5-3.4% of all poisonings1. Mortality from mushroom poisoning is high, especially in spring and autumn, and is often caused by amanita species. Amatoxin, which is mainly responsible for poisonings; It affects cells with rapid cell turnover, such as the liver, kidney and intestinal system. Although toxins affect the whole body, liver and kidney failure in particular are the main causes of mortality and morbidity in these patients. The average half-life of alpha-amanitin is 22 hours, 85% of which is excreted in the urine within six hours. Acute tubular necrosis (ATN) may occur as a result of the absorption of toxins from the proximal tubule2. In our case, the fungal species was not specified. However, the history and clinical findings developed after mushroom ingestion and acute renal failure was observed.

While fungi can cause mild symptoms such as nausea and vomiting, they can also cause serious symptoms such as kidney and liver failure. The duration of signs and symptoms varies depending on the type of toxin contained in the mushroom. Mushroom poisonings are classified into two groups: 'those with early symptoms (first 6 hours)' and 'those with late symptoms (later than 6 hours)'. The Amanita group causes acute gastroenteritis syndrome within a few hours and delayed-onset renal failure within a week. Three to six days after mushroom consumption, patients begin to experience symptoms of renal failure, particularly oliguria and anuria. Alpha-amanitin and beta-amanitin, the most poisonous amatoxins, are held responsible for hepatorenal syndrome[3]. Our case was a case with late symptoms and signs of acute renal failure.

The most serious mushroom poisonings occur with hepatotoxic species, the nephrotoxic ones being Cortinarius orrelanus and Paxillus involutus[4-6]. In order to minimize toxic damage to highly sensitive cells, detoxification treatment should be started early[7].

Dialysis is often necessary in case of ingestion of Amanita group mushrooms to restore kidney function. Supportive dialysis is typically required for two to five weeks, but in one case was required for six months.If large amounts of fluid cannot be removed with such conservative methods, ultrafiltration or dialysis treatment may be required[8]. Dialysis does not accelerate the recovery of acute renal failure. Initial studies did not provide data indicating that early dialysis improved prognosis[9].

It was stated that in Amanita proxima poisoning, which included fifty-three cases, acute renal failure developed in 14 of the patients and hemodialysis was successfully performed in 10 of them. However, the hemodialysis procedure performed here is not for the removal of the toxin, but for the treatment of acute renal failure[10] . Sınce the patıent had acıdosıs, an emergency hemodıalısıs catheter was ınstalled and he was hemodıalızed. After 1500 uf was made. Medical treatment has started. Our case was discharged with full recovery after follow-up and treatment.

Conclusion

As a result of mushroom poisoning, late clinical kidney failure can be seen. Mushroom poisoning should not be forgotten in patients brought to the emergency room with coma. If it is not possible to follow-up these patients after the complaints that occur in the first days, they should be informed about possible late complications. Cultivated mushrooms should be preferred to prevent poisoning.

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Case Report
Eurasian Journal of Toxicology

Nivik Herb - Arum Maculatum – Poisoning

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Abstract

Nivik grass (Arum maculatum), which belongs to the Araceae family, is also known as snake's pillow, bear's ear, shadbush and kabargan. In the international literature, it is known as bobbins snakeshead, Adam and Eve, lords-andladies, arum, naked girls, soldiers diddies and wake robin.

Keywords: Nivic weed, mucosal damage, symptomatic treatment, public education

Introduction

Due to its strong acid content, it has an irritant effect on mucous membranes and may cause gastrointestinal side effects. Due to its similarity with other herbs such as spinach (Figure 1.a. b) , which is widely consumed, it can be consumed inadvertently in nature. When consumed after boiling or drying, the effects are less pronounced. It is common in the Black Sea and Mediterranean regions. Plant roots are used for antipyretic and parasite treatment among the people In the international literature, it is known as bobbins snakeshead, Adam and Eve, lords-andladies, arum, naked girls, soldiers did dies and wake robin[1-3].

Case

Our 40-year-old female patient bit the nivic grass which she had eaten about 30 minutes ago thinking it was spinach, but she did not swallow it (Figure 1c.). At the initial evaluation, general condition was good, conscious, coherent, and vital signs were stable. Physical examination revealed hyperemia in the mouth and other findings were normal. After 4 hours of follow-up, the patient did not have any complaints and was informed about anaphylaxis and other possible complications and sent with recommendations. No complaint developed in 24-48 hours follow-up.

Discussion

The plant contains capsaicin (analgesia), lectin (antiparasitic) and saponin oxalate (mucosal damage). The saponin in the seasonally blooming red-orange fruits may cause allergic reactions. Studies have also reported that allergic reactions did not develop in patients who consumed the plant by boiling it. Oxalate-containing plants bind with calcium. Decreased calcium affects the heart, skeleton, kidney and nervous system. Cases of vomiting, seizure, spasticity, dyspnea, angioedema and death have been reported [3,4].

All parts of this wild plant have a strong irritating effect on mucous membranes. However, if it is boiled or dried for a long time, it becomes more harmless. Skin, mouth, tongue and this condition, which irritates the throat, results

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1a 1b 1c

Photo 1a: Nivik herb
1b. Spinach
1c. The nivik herb that the subject took into his mouth
(Pictures taken from the archive of Ali Karakuş)

in difficulty breathing and stomach discomfort, is caused by the plant the saponin oxalates it contains are responsible. [5] In our case, mucosal edema and a tingling sensation occurred after ingestion. The symptoms subsided within an hour.

A. maculatum poisoning. previously reported In cases of severe poisoning, vomiting, seizure, spasticity, difficulty speaking, breathing. Symptoms such as stenosis have been observed.[2] The patient followed complained of numbness and swelling in the mouth.

Medicinal properties of Arum maculatum are proinflammatory, analgesic, antibacterial and antioxidant.[6] Our subject accidentally ingested it.

Since there is no antidote, calcium carbonate, magnesium and diuresis treatments can be applied as symptomatic treatment to precipitate oxalate. Patients without symptoms can be discharged with recommendations after 4-6 hours of observation[3,4].Our patient, who did not develop any complications, was discharged with recommendations after six hours of observation.

Conclusion

Weeds commonly encountered in nature should be considered toxic until proven otherwise, and the public should be made aware of anaphylaxis and other fatal conditions and should not consume unfamiliar foods. We believe that thus the cases of poisoning will decrease.

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Erratum

Eurasian Journal of Toxicology

Epidemiological pattern of Extracorporeal methods in acute poisoning: A-five-year Study

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In the first issue to be published in 2024, the word pattern was mistakenly written as attern in the article by Dr. Mitra Rahimi and colleagues titled "Epidemiological Attern of Extracorporeal Methods in Acute Poisoning: A-Five-Year Study." The corrected version is "Epidemiological Pattern of Extracorporeal Methods in Acute Poisoning: A-Five-Year Study." We apologize for this situation.

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