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Editorial

Değerli Okuyucular;

"Eurasian Journal of Toxicology" dergimizin üçüncü sayısı ile birlikte 2019 yılını kapatıyoruz. Editörler olarak derginin kuruluşu sırasında klinik toksikoloji alanında bilimsel literatüre katkı sağlayabilecek çalışmaların paylaşılabileceği şeffaf, bağımsız ve kaliteli bir ortam yaratabilmeyi hedeflenmiştik. Yayın hayatımıza bu yıl başlamamıza rağmen dergimizin birinci yılını bilimsel açıdan oldukça dolu geçirdik ve geçen sürenin ardından başlangıçta koyduğumuz hedefimize ulaştığımızı görmekten dolayı mutluyuz. Bir sonraki hedefimiz olan ulusal ve uluslararası indekslerce taranan saygın bir bilimsel dergi olma amacımıza da siz değerli meslektaşlarımızın önemli ilgi ve katkıları sayesinde emin adımlarla ilerlemekteyiz.

Dergimizin bu sayısında da sizleri yine bilimsel açıdan doyurucu bir içerik bekliyor. A vitamini ve antiviral ilaç toksisiteleriyle ilgili iki ilginç derleme sizlerle buluşacak. Yaşlanan nüfusumuzla birlikte daha fazla ilgi çeken geriatrik zehirlenmelerle ilgili bir orijinal araştırma makalesi dahil olmak üzere toplam dört araştırma makalesine ve yine sıra dışı iki vaka sunumuna bu sayımızda ulaşabilirsiniz.

Birinci yılımızı tamamladığımız bu sayıyla birlikte, gönüllülük ilkesi ile hiçbir beklenti olmaksızın çalışmaları yürüten derginin yayın kurulu ve danışma kurulu üyelerine ayrıca dergiye sağladıkları katkılardan dolayı hakem ve yazarlara, derginin kuruluşunda ve gelişmesinde emek harcayan başta Acil Tıp Uzmanları Derneği (ATUDER) yönetim kurulu başkanı Prof. Dr. Başar Cander olmak üzere tüm ATUDER yönetim kuruluna teşekkür ederiz.

İyi Okumalar

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Antiviral Drugs and Their Toxicities

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Abstract

Developments in antiviral agents have led to significant progress in the treatment of infections caused by herpes simplex virus 1-2, varicella-zoster virus (VZV), cytomegalovirus, influenza A and B, and human immunodeficiency virus (HIV). There are several antiviral drug therapies that are widely used today. These antiviral drugs are examined under four main headings: drugs effective against influenza viruses, drugs effective against herpes viruses, anti-HIV drugs and immunomodulators in antiviral therapy. Toxicities of these drugs are also examined in four main headings: toxicity of drugs that are effective against herpes viruses, toxicity of drugs effective against influenza viruses, toxicity of antiretroviral drugs and toxicity of other antiviral agents. Under these main headings, antiviral drugs and toxicities of these drugs will be analyzed in more detail. The side effects and toxicities of these drugs should be well known and if such a situation is encountered, it would be more appropriate to choose another antiviral treatment that may have less side effects and toxicity for the patient if necessary.

Key words: Antiviral drugs, side effects, toxicity

Özet

Antiviral ajanlardaki gelişmeler, herpes simpleks virüs 1-2, varisella-zoster virüs, sitomegalovirüs, influenza A ve B ve insan immün yetmezlik (HIV) virüsü kaynaklı enfeksiyonların tedavisinde önemli ilerleme sağlamıştır. Günümüzde yaygın olarak kullanılan çeşitli antiviral ilaç tedavileri vardır. Bu antiviral ilaçlar dört ana başlık altında incelenir: influenza virüslerine karşı etkili ilaçlar, herpes virüslerine karşı etkili ilaçlar, anti-HIV ilaçları ve antiviral tedavide kullanılan immünomodülatörler. Bu ilaçların toksisiteleri ayrıca dört ana başlıkta incelenmiştir: herpes virüslerine karşı etkili ilaçların toksisitesi, influenza virüslerine karşı etkili ilaçların toksisitesi, antiretroviral ilaçların toksisitesi ve diğer antiviral ajanların toksisitesi. Bu derlemerde, ana başlıklar altında, antiviral ilaçlar ve bu ilaçların toksisiteleri daha ayrıntılı olarak analiz edilecektir. Bu ilaçların yan etkileri ve toksisiteleri iyi bilinmeli ve eğer böyle bir durumla karşılaşılırsa, gerekirse hasta için daha az yan etkisi ve toksisitesi olabilecek başka bir antiviral tedavi seçmek daha uygun olacaktır.

Anahtar kelimeler: Antiviral ilaçlar, yan etki, toksisite

Introduction

Developments in antiviral agents have led to significant progress in the treatment of infections caused by herpes simplex virus 1-2, varicella-zoster virus (VZV), cytomegalovirus, influenza A and B, and human immunodeficiency virus (HIV).

The best drugs used against herpes simplex virus and cytomegalovirus infections are aciclovir, penciclovir and ganciclovir. The effects of these drugs are not optimal when administered orally. Higher oral drug doses may be required to provide the appropriate blood and tissue dose to inhibit viral replication. Three prodrugs have been produced for drug formulation and product development: valaciclovir, famciclovir and valganciclovir. Valine ester, which leads to increased gastrointestinal absorption of a drug, was added to aciclovir and ganciclovir to come up with valaciclovir and valganciclovir, respectively. When the drug reaches the liver, the valine is hydrolyzed and removed, which is followed by the formation of aciclovir and ganciclovir.

ANTIVIRAL DRUGS

1- Drugs Effective Against Influenza Viruses

Influenza is an acute and contagious disease caused by the influenza virus (usually A and sometimes B viruses) that affects the respiratory system, which is characteristically seen in the form of epidemics.

There are two main groups of drugs for influenza virus infections, which are used in prophylaxis or treatment. These two groups of drugs are amantans (amantadine and rimantadine), also known as M2 inhibitors, and the newer group of neuraminidase inhibitors (zanamivir and oseltamivir).

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a) M2 inhibitors: Drugs developed in the early 1960s and used in infections caused by influenza A viruses are amantadine and rimantadine. M2 is found only in the influenza virus and is an acid-activated ion channel. It is a membrane protein necessary for the release of nucleocapsid after the fusion of the virus with the endosomal membrane. After this inhibition, they prevent the intake of the virus into the host cell through endocytosis, the uncoating of the virus, the coming together of viral products and the virion assembly. The second mechanism is associated with the fact that they reduce the lysosomal pH, following the concentration of amantadine and rimantadine in lysosomes[1–4].

b) Neuraminidase inhibitors: Influenza viruses all have two surface glycoproteins: hemagglutinin and neuraminidase. These antigens identify the specific type of the influenza. Zanamivir and oseltamivir are neuraminidase inhibitor drugs currently used in the clinic. Both of these drugs are sialic-acid analogues, but they potently and specifically inhibit neuraminidase found in both influenza A and influenza B viruses reversibly[5,6].

2- Drugs Effective Against Herpes Viruses

Antivirals are drugs that kill viruses or inhibit their reproduction. In order for an antiviral agent to be effective, it must prevent the virus from multiplying or kill the virus directly without affecting the host cell.

Viruses are made up of genetic materials in the structure of single or double-stranded DNA or RNA. On the outer side of the virus, there is a protein mantle called capsid. Some viruses have another structure called envelope other than capsid, which is composed of lipoproteins and has antigenic properties. Viruses can be described as intracellular parasites. They use the host cell (bacterial, plant or animal cell) that is more advanced than they are to produce their viral proteins and genetic materials[7].

The herpes virus family consists of morphologically similar enveloped and large viruses, containing large, double-helix DNAs. Following the primary infection, they remain latent in the host and can be reactivated, which are some of their most important characteristics[8].

Herpes virus family classification

A- Alpha herpes viruses:

1- Simplex viruses (HSV)
-Herpes Simplex Virus-Type 1 (HSV-1)
-Herpes Simplex Virus-Type 2 (HSV-2)

2- Varicella viruses
-Varicella-Zoster Virus (VSV)

B- Beta Herpes Viruses:
1- Cytomegalovirus (CMV)
2- Muromegalovirus
3- Roseolovirus

C- Gamma Herpes Viruses:
1- Epstein-Barr virus (EBV)
2- Rhadinoviruses

Drugs Effective Against Herpes Viruses

a) Aciclovir and Valaciclovir: These are drugs that block viral DNA synthesis[7]. The selectivity of their effect depends on their interaction with two viral proteins. Viral thymidine kinase is the first of these proteins. It is responsible for ensuring the entry of the drug into the cell and the initial phosphorylation of the drug. The interaction with the second protein is that aciclovir in the cell gets into competition with endogenous deoxyguanosine triphosphate (dGTP).

b) Famciclovir and Penciclovir: Penciclovir is an acyclic guanine nucleotide analogue. The diacetyl derivative manufactured to improve the oral bioavailability of penciclovir is famciclovir8. Penciclovir inhibits the viral DNA synthesis of HSV and VZV viruses. In infected cells, viral thymidine is phosphorylated by kinase and transformed into triphosphate, which is a competitive inhibitor of the DNA polymerase enzyme[9].

c) Ganciclovir and Valganciclovir: The prodrug of ganciclovir is valganciclovir. Ganciclovir inhibits viral DNA synthesis.

d) Cidofovir: Cidofovir is a nucleotide analogue of cytidine10. It inhibits viral DNA synthesis and subsequently slows or inhibits the lengthening of the DNA strand.

e) Foscarnet: Foscarnet is an inorganic pyrophosphate analogue (trisodium phosphonoformate). By inhibiting viral nucleic acid synthesis, foscarnet indirectly inhibits the DNA polymerase enzyme of the herpes virus and the HIV reverse transcriptase enzyme.

f) Docosanol: Docosanol prevents invitro replication of several viruses that carry lipid envelopes. It does not directly inactivate HSV but prevents the fusion between the cell membrane and the virus envelope, and it prevents the virus from entering the cell.

g) Fomivirsen: Its effect is on mRNA in the early protein synthesis process of CMV. Its effect on mRNA prevents replication of the virus and its binding to the cell.

h) Trifluridine: Thymidylate synthetase irreversibly inhibits trifluridine monophosphate, and trifluridine triphosphate is a competitive inhibitor of thymidine triphosphate.

i) Idoxuridine: It is an iodine thymidine analogue and inhibits the replication of the DNA virus.

3- Anti-HIV Drugs

Acquired immune deficiency syndrome (AIDS) is a fatal, chronic, infectious disease that occurs as a result of the transmission of the human immunodeficiency virus (HIV), and the increasing suppression of the immune system. There is no cure yet to eliminate the virus in HIV infection, but there are drugs that control the proliferation of the virus. These drugs are called "Antiretroviral Drugs," and the treatment with these drugs is called "Antiretroviral Treatment." There is still no definitive solution for the treatment of the disease. With the drugs in use, it is possible to control the disease but not cure it. However, it is reported that life expectancy can be extended with intensive treatment11.

Today, antiretroviral drugs are examined in four groups: nucleoside reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors (FIs).

a) Nucleoside Reverse-Transcriptase Inhibitors (NRTIs): The phosphorylated active metabolites of the drugs in this group compete to bind to the viral DNA. They inhibit HIV's RT enzyme by competing and act as a strand that ends the DNA synthesis12. Drugs in this group include Zidovudine (ZDV, AZT) (Retrovir), Didanosine (ddl) (Videx), Zalcitabine (ddC) (HIVID), Stavudine (d4T) (Zerit), Lamivudine (3TC) (Epivir), Abacavir (ABC) (Ziagen), Emtricitabine (FTC) (Emtriva), and Tenofovir Disoproxil Fumarate (TDF) (Viread). Amdoxovir, Apricitabine and Elvucitabine are drugs whose experimental studies continue.

b) Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs): These drugs bind directly to the parts of the RT enzyme that are different from the nucleoside-binding region of it. Resistance to these drugs develops rapidly in general. For this reason, they are not preferred in monotherapy except in special cases. Drugs in this group include Nevirapine (NVP) (Viramune), Delavirdine (DLV) (Rescriptor), and Efavirenz (EFV) (Sustiva). Calanolide A, Etravirine, and Rilpivirine are the drugs with continuing experimental studies.

c) Protease Inhibitors (PIs): Protease inhibitors constitute the most effective class among antiviral drugs. The viral protease enzyme is their main target. As a result of the inhibition of viral proteases, the division of gag-pol polyprotein is prevented, which results in the formation of non-infective viral particles. Drugs in this group include Saquinavir mesylate (SQV) (Invirase), Ritonavir (RTV) (Norvir), Lopinavir, Indinavir (IDV) (Crixivan), Nelfinavir mesylate (NFV) (Viracept), Amprenavir (APV) (Agenerase), Fosamprenavir Calcium (FOS-APV) (Lexiva), Atazanavir sulfate (ATV) (Reyatase), Tipranavir (TPV) (Aptivus), and Darunavir (Prezista).

d) Fusion Inhibitors: The effect of fusion inhibitors is to prevent the entry of HIV into healthy T cells in the body. Entry inhibitors take effect by binding to proteins on the surface of HIV or T cells. In order for HIV to bind to T cells, HIV's outer membrane proteins need to bind to the surface proteins of T cells. Entry inhibitors prevent this event. Some of the entry inhibitors target the gp120 or gp41 proteins on the surface of HIV. Drugs in this group include Enfuvirtide (ENF) (Fuzeon), Maraviroc, and Vicriviroc.

e) Combined Preparations: Atripla (Efavirenz + Emtricitabine + Tenofovir), Combivir (Retrovir + Epivir), Epzicom (Abacavir + Epivir), Trizivir (Abacavir + Zidovudine + Lamivudine), Truvada (Emtricitabine + Tenofovir), and Kaletra (Lopinavir + Ritonavir).

4- Immunomodulators in Antiviral Therapy

Immunomodulatory drugs have been used for years as a hope to treat cancer and infectious diseases.

Immunomodulators can be grouped under 6 groups:
a) Natural cytokines (colony stimulant factors, interleukins, interferons, chemokines and thymic hormones)
b) Monoclonal antibodies and receptor antagonists
c) Immunoglobulins
d) Steroids
e) Synthetic compounds (thalidomide, imiquimod, and so forth)
f) Anti-inflammatory anticoagulants (activated protein C).

TOXICITY OF ANTIVIRAL DRUGS

1- Toxicity of Drugs Effective Against Herpes Viruses

a) Aciclovir (Hernovir): It has mutagenic characteristics because of its effects on the cell DNA. It does not have teratogenic and carcinogenic effects if used for a long time. Although its acute toxicities are relatively low in oral uses of less than 1 mg/kg, cases undergoing excessive intravenous therapy such as 80 mg/kg have been reported to experience excessive major toxic effects. It has also been reported that hallucinations occur in high dose use. Edema, arthralgia, sore throat, and weakness are some of the other common effects, in addition to CNS findings such as agitation, vertigo, confusion, and dizziness. From time to time, heavier clinical presentations can be seen, which include Stevens-Johnson syndrome, and toxic epidermal necrolysis. Coma, convulsions, neutropenia, leukopenia, crystalluria, anorexia, hepatitis and even anaphylactic reactions can be seen as rarer

side effects. In the urogenital system, a high level of urea and creatinine causes side effects that start with hematuria and then may lead to renal failure. Encephalopathy, and pain and irritation at the injection site may be seen in 1% of patients among additional side effects when they are given intravenous therapy[13–15].

b) Cidofovir (Vistide): Its effects are similar to those of ganciclovir and foscarnet, and renal insufficiency with proteinuria is its most important side effect. The effects cause rash, headaches, fever and even iritis and hypotonia[16].

c) Docosanol (Abreva 10%): It is well tolerated at the onset of treatment. Prodromal findings are also observed during the first 12 hours of treatment[17].

d) Famciclovir (Famvir): It inhibits DNA polymerase, and reduces recovery time and postherpetic neuralgia, especially in elderly patients[18].

e) Foscarnet (Foscavir): It reduces glomerular filtration rate in kidneys and increases serum creatinine. Its most important effect on the renal system is the fact that it causes acute and chronic renal insufficiency. It also causes frequent side effects of hypokalemia, hypocalcemia, hypomagnesemia, phosphatemia and CNS. Direct retinal toxicity, intravitreal bleeding, and endophthalmia are its potential side effects. Its safety in pregnant women and children is uncertain because it is mutagenic and can cause skeletal and dental anomalies[19].

f) Ganciclovir (Cytovene): It often and substantially causes hematologic reactions such as granulocytopenia, neutropenia, thrombocytopenia and anemia. Phlebitis accompanied by pain, redness, and itching may occur in parenteral use. Serum urea and creatinine may also be elevated. Ganciclovir has chronic toxic effects. These effects are thought to be carcinogenic, mutagenic and teratogenic, and inhibit spermatogenesis. For this reason, they are considered to be among cytotoxic drugs.

g) Idoxuridine (Herpes, Stoxil, Dendrite): It acts on viral and host cell DNAs and is highly toxic. Irritation, pain, pruritus, inflammation, eyelid edema, and photophobia are its rare allergic reactions[20].

h) Penciclovir (Denavir): It acts as a placebo in terms of side effects. Its cytotoxicity is negligible.

i) Trifluridine (Viroptic): Stinging in the eye, burning sensation, and palpebral edema are its common acute side effects. Less commonly, keratopathy and hypersensitivity reactions may occur.

j) Tromantadine (Viru-Merz)

k)Valaciclovir (Valtrex): It has side effects such as nausea, vomiting, diarrhea, and headaches. In 0.1% of patients, it causes CNS and hematopoietic side effects such as coma, convulsion, neutropenia, leukopenia, tremor, ataxia, and encephalopathy. It leads to thrombotic thrombocytopenic purpura and hemolytic uremic syndrome[13].

l) Valganciclovir (Valcyte): Neutropenia, anemia, and thrombocytopenia can occur. It may cause myelosuppression if used for a long time. Its side effects on GIS are diarrhea, nausea, vomiting, and abdominal pain. Fever, headache, insomnia, paresthesia, and peripheral neuropathy occur in the CNS, and especially retinal detachment occurs in the eye[21].

m) Vidarabine (Vira A, Ara A): Its toxic side effects are rare. Conditions such as vomiting, leukopenia, and thrombocytopenia may be seen, although rarely, in high dose intravenous therapy[22].

2- Toxicity of Drugs Effective Against Influenza Viruses

a) Amantadine (Symmetrel): Irritability, anxiety, agitation, insomnia, concentration disorder, lisping, ataxia, depression, and hallucinations may often occur as CNS side effects. GIS findings such as nausea and constipation may also be observed. These effects are intensive within 48 hours of drug use and decreases over time. Its safety in pregnant women is not certain[23].

b) Rimantadine (Flumadine): Its side effects are mostly on GIS and CNS and are less common than those of other influenza drugs. Nausea, stomach pain, irritability, fatigue, sensitivity to light, sleep disturbance, and difficulty in concentration have been observed in 6% of patients using the drug[23].

c) Oseltamivir (Tamiflu): Nausea, vomiting, diarrhea, abdominal pain, and headaches are common, but less commonly, serious effects such as hepatitis, increased liver enzymes, allergic reactions leading up to anaphylaxis, and even Stevens-Johnson syndrome may also occur. Cases of toxic epidermal necrolysis, arrhythmia, convulsions, confusion, increased diabetes, and hemorrhagic colitis have also been reported in recent years. Abnormal behaviors and hallucinations have been added to its neurological effects in recent years. As a matter of fact, it was observed that oseltamivir-related deaths occurred between 2000 and 2004 for various reasons. Its pediatric safety is unclear and attention should be paid to behaviors such as delirium and hallucinations. Its safety in pregnant women is not certain, either[24].

d) Zanamivir (Relenza): Although generally well tolerated in children and adults, it has been reported to cause wheezing and bronchospasm. For this reason, it is not preferred to be

used in people with respiratory diseases. It is comfortable to use in terms of drug interactions, and there is no information as to whether it is mutagenic, teratogenic or carcinogenic[25].

3- Toxicity of Antiretroviral Drugs

If we are to generalize the side effects caused by retroviral drugs, they vary depending on the individual, the drug used with it, the ethnicity, and the amount of alcohol consumption. Their common side effects include abdominal pain, alopecia, anemia, asthenia, diarrhea, vertigo, fanconi syndrome, flatulence, headache, hepatitis, hyperbilirubinemia, hypercholesterolemia, hyperpigmentation in palms, soles and nails, insomnia, liver failure, weakness, mental confusion, myalgia, encephalomyelitis, myopathy, nausea, neutropenia, intraoral ulcers, pancreatitis, paresthesia, peripheral neuropathy, redness, renal insufficiency, somnolence, Stevens-Johnson syndrome, vomiting, dry mouth, dry skin, and deterioration in the sense of taste.

A- Nucleoside Analog Reverse-Transcriptase Inhibitors (NARTIs)

a) Zidovudine (Retrovir, Retrovis) (AZT, ZDV): Nausea, headaches, discoloration of the feet and fingernails are its common acute toxic effects. Bone marrow suppression and anemia are also its serious side effects. Its unexpected side effect is gamma DNA polymerase sensitivity in cell mitochondria. It has additive or synergistic interaction with many drugs for treating HIV. However, aciclovir and ribavirin reduce the effect of AZT. Its hepatic glucuronidation is inhibited and its toxic effects increase when used with aspirin, indomethacin and trimethoprim.

b) Didanosine (Videx, Videx EC): Diarrhea, nausea, vomiting, abdominal pain, fever, headache, and redness are its common side effects. In addition to these, peripheral neuropathy, pancreatitis, retinal changes, optic neuritis, and liver dysfunctions may also occur rarely. These conditions worsen even further if alcohol is used with it. The development of resistance to the drug is slower than that to zidovudine. It causes gene mutations[26].

c) Zalcitabine (Hivid): Nausea and headaches are frequently seen at the onset of treatment. Peripheral neuropathy, intraoral ulcers, esophageal ulcers and rarely pancreatitis are observed in more than 33% of patients with progression of the disease. It causes mutations.

d) Stavudine (Zerit, Zerit XR): Peripheral neuropathy is a serious side effect of it that also requires reducing the drug dose. In laboratory studies, it has been observed to be genotoxic but not carcinogenic at clinical doses. Lipodystrophy is one of the conditions frequently caused by antiviral drugs.

e) Lamivudine (Epivir): It has been found, according to the results of many mutagenic tests, that it does not cause any mutagenic activity at the dose of treatment. Cases requiring to see a doctor are redness, stomach pain, burning and numbness in toes and fingers[27].

f) Abacavir (Ziagen): During treatment, fatal hypersensitivity reactions, GIS findings such as fever, redness, weakness, nausea, vomiting, diarrhea and abdominal pain, and respiratory system findings such as pharyngitis, dyspnea and cough occur. Hypersensitivity reactions strongly correlate with HLA-B 5701, and this relationship is stronger in western countries. Hepatomegaly and lactic acidosis are also common serious side effects[28].

g) Emtricitabine (Emtriva): Toxicity of this drug is not usual in clinical studies. It does not cause a mutagenic effect. Diarrhea, headache, nausea and redness are its side effects related to treatment. These symptoms are usually mild or moderate. These conditions increase as the treatment is continued. It has severe side effects such as pancreatitis, hepatitis and lactic acidosis, while it causes hyperpigmentation on soles and palms.

B- Nucleotide Analog Reverse-Transcriptase Inhibitors (NTARTIs)

Nucleoside analogues are transformed into nucleotide analogues in the body, and this group of drugs have been shown to cause less toxicity.

a) Tenofovir (Viread): Although it causes unease in the stomach, diarrhea, vomiting, decreased appetite and gas complaints, these effects are not serious. It causes effects similar to those of adefovir and cidofovir. It has been reported in in vitro studies16 that it does not cause renal tubular damage in humans, but acute renal failure and Fanconi Syndrome have been reported in rare cases with tenofovir[29].

C- Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs)

a) Neviparine (Viramune): Approximately 13% of patients have mild or moderate redness, and 1.5% have been observed to have severe and life-threatening skin reactions. These are Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity30. Moreover, severe liver toxicity is observed in the first six months of the use of neviparine.

b) Delavirdine (Rescriptor): Moderate and severe redness is a common side effect in 20% of patients. Moreover, nausea, weakness, headache, and liver toxicity findings have been reported, but it does not cause fatal hepatitis. Severe skin lesions such as erythema multiforme and Stevens-Johnson syndrome may be seen, although rarely.

c) Efavirenz (Sustiva, Stacrin): Psychiatric findings such as insomnia, confusion, loss of memory and depression may occur. In addition to these, redness in the skin, nausea, headache, and dizziness may also occur. It can cause fetal anomaly and therefore should not be used in pregnant women. It is also a drug that is not completely safe for children.

D- Protease Inhibitors

a) Saquinavir (Fortavase): Acute effects are mostly findings of GIS irritation such as moderate diarrhea, nausea and abdominal uneasiness. Its oral bioavailability is low when used alone. It interacts with drugs that interact with the cytochrome P450 3A4 enzyme. It causes lipodystrophy.

b) Tipranavir (Aptivus): Its causes quite a high number of side effects[31].

c) Ritonavir (Norvir): It interacts with drugs that interact especially with the cytochrome P450 3A4 enzyme. Its frequently seen acute effects are weakness, fatigue, vomiting, stomach uneasiness, diarrhea, headache, and vertigo. It may also cause increased blood sugar, increased cholesterol, frequent urination, and thirst[32].

d) Nelfinavir (Viracept): It causes diarrhea, abdominal pain and gas complaints in more than 1% of patients, and weakness, frequent urination, mouth ulcers and hepatitis in 0.01–0.1% of patients. Nephrolithiasis, arthralgia, leukopenia, pancreatitis and severe allergic reactions may occur less commonly. It increases cholesterol and triglycerides.

e) Lopinavir (Kaletra): Severe diarrhea and nausea are seen in more than 27% of patients. Moreover, frequently observed acute effects are abdominal pain, asthenia, headache, vomiting, redness (mostly in children), high liver enzymes, and hyperlipidemia[32]. Lopinavir is used in combination with ritonavir.

f) Indinavir (Crixiva): It causes side effects such as calculous formation, crystalluria, hyperlipidemia, hyperbilirubinemia, hyperglycemia, and lipodystrophy. It has also been reported to cause dry skin, lip dryness and rarely GIS findings.
g) Fosamprenavir (Lexia): It changes hyperglycemia and lipid profile, as well as causing symptoms such as nausea, vomiting, diarrhea, weakness, paresthesia, and headache. It causes the same effects as those of amprenavir[33].

h) Darunavir (Prezista): It is used in combination with ritonavir. Its effects are like those of ritonavir[32].

i) Atazanavir (Reyataz): Lipodystrophy, high cholesterol and triglyceride, and hyperbilirubinemia are the side effects that it causes frequently. Its effect on blood sugar is not clearly known[34].

j) Amprenavir (Agenerase): It causes mild diarrhea and self-limiting skin rashes[33].

E- Fusion Inhibitors

a) Enfuvirtide (Fuzean): In rare cases, pain, erythema, cysts, nodules, itching are seen at the injection site. Especially in the first week of use, peripheral neuropathy, insomnia, depression, cough, dysphonia, anorexia, arthralgia, bacterial infection and eosinophilia are seen in almost all patients. Hypersensitivity reactions such as skin redness, fever, nausea, vomiting, shivering, hypotension and elevated liver transaminases have been observed; and anaphylaxis has been observed, which involve these findings accompanied by respiratory distress and glomerulonephritis[35].

4- Toxicity of Other Antiviral Agents

a) Adefovir dipivoxil (Preveon, Hepsore): The drug, which is used to treat hepatitis B, has not been approved for HIV by the FDA. It causes unease in the stomach, diarrhea, vomiting, decreased appetite and gas complaints, but these are not serious effects. It causes effects similar to those of tenofovir and cidofovir16. It causes proteinuria, glucosuria, hypophosphatemia, acidosis and azotemia and even cause tubular dysfunction. It should not be used in pregnant women because it can cause anomalies[36].

b) Fomivirsen (Vitravene): It is used locally in the treatment of CMV retinitis. Its side effects are mostly ocular, and it may cause iritis, cataracts and elevated intraocular pressure in 25% of patients.

c) Imiquimod (Aldara): Irritation, burning and redness in the skin are its common side effects during treatment.
d) Inosine: It has been reported to cause moderate GIS findings, such as abdominal uneasiness and nausea. It has been observed to increase the production of uric acid, a natural antioxidant, and prevent axon degeneration by binding peroxynitrite that occurs in multiple sclerosis[37].

e) Interferon (Intron A, Roferon A, Infergen, Alferon N): The risks and side effects of this drug are almost nonexis-

tent. Successful results are obtained in preventing malignant cells from spreading and in persistent infections. Its known side effects are hypertension, dyslipidemia, hyperglycemia, proteinuria, azotemia, interstitial nephritis, hepatotoxicity, pneumonia, and peptic ulcers. This immune-suppressive drug reacts with other drugs. Fever, shivering, weakness and myalgia, which occurs 7–12 hours after the first injection, lasting up to 12 hours, are seen[38].

f) Podophyllotoxin (Etoposide): It lowers blood pressure. Hair loss, pain and redness at the intravenous therapy site, constipation or diarrhea, metallic taste in the mouth, and bone suppression may be seen. As a result, it can cause leukopenia, anemia and thrombocytopenia and consequent bleeding in the bone marrow[39].

g) Ribavirin (Virazole, Rebetol, Copegus): Its serious side effect is hemolytic anemia. It has also been observed to worsen cardiac diseases, but the mechanism of this is not yet known. Although it does not interact with DNA, it has been reported to inhibit DNA synthesis depending on the dose and cause a serious teratogenic effect. There are also clinical studies claiming that it facilitates tumor formation, that it probably has genotoxic effects and that it causes breathing difficulties due to its use.

In conclusion, there are several antiviral drug therapies that are widely used. Although each of the agents we use in antiviral therapies has many different side effects, sometimes these therapies can lead to many different toxic clinical presentations. The side effects and toxicities of these drugs should be well known and if such a situation is encountered, it would be more appropriate to choose another antiviral treatment that may have less side effects and toxicity for the patient if necessary.

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Review Article

Eurasian Journal of Toxicology

Hypervitaminosis A

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Abstract

Vitamin A is essential for life and is the first found vitamin. It has many effects on growth, reproduction, vision and immune system. Nowadays, there is a risk of intoxication following the increase in intake of vitamin A ,taken with foods, with additional supplementary drugs Many studies have been conducted on the deficiency of vitamin A and although adequate measures have been taken in developed and developing countries, it is difficult to estimate the health risks to be created in the future due to the lack of adequate studies in terms of vitamin A intoxication and failure to take necessary measures on the subject.

Acute intoxication has been reported rarely, especially in young adults, as vitamin A is highly tolerated by the body in the acute phase. Intoxication, which mostly develops after chronic exposure to high-dose vitamin A, affects many organs.

Further epidemiological studies are needed to be able to understand how serious public health problem vitamin A intoxication without specific treatment is.

Key words: Retinoic asid, Toxication, Vitamin A

Özet

A Vitamini yaşam için esastır ve ilk bulunan vitamindir. Büyüme, üreme, görme ve bağışıklık sistemi üzerinde birçok etkisi vardır. Son zamanlarda, gıdalarla ve ek ilaçlarla artmış A vitamini alımına bağlı zehirlenmelerle karşılaşılmaktadır. A vitamini eksikliği konusunda birçok çalışma yapılmış bu konuda gelişmiş ve gelişmekte olan ülkelerde yeterli önlemler alınmıştır. Ancak A vitamini zehirlenmesi konusunda yeterli araştırma yapılmaması ve konuyla ilgili gerekli önlemlerin alınmaması nedeniyle gelecekte ortaya çıkacak sağlık risklerini tahmin etmek zordur.

Özellikle genç erişkinlerde akut zehirlenme nadiren bildirilmiştir, çünkü A vitamini akut fazda vücut tarafından oldukça tolere edilir. Çoğunlukla yüksek dozda A vitaminine kronik maruz kalmadan sonra gelişen zehirlenme birçok organı etkiler.

A vitamini zehirlenmesinin, spesifik tedavisinin yapılmadığında ne kadar ciddi bir halk sağlığı problem haline gelebileceğini anlamak için ileri epidemiyolojik çalışmalara ihtiyaç vardır.

Anahtar kelimeler: A vitamini, Retinoik asit, Zehirlenme

Short History

Vitamin A (retinoic acid) is a fat-soluble substance necessary for growth, reproduction, immunity and vision. Although it is not known exactly when vitamin A was discovered, it was observed in a study conducted in 1881 that the growth and development of the subjects regressed, the immune system weakened and severe eye inflammation developed after the removal of natural fats in the nutrients of animals. Then, with the addition of natural fats to their diets, it was possible to say that a fat-soluble substance is essential for life after rapid recovery of animals[1]. After its chemical structure was first discovered in 1931 many studies on the biological process of vitamin A and its derivatives on metabolism have revealed that vitamin A is essential for life [2]. After the discovery of its antioxidant properties, it has started to be used in the treatment of oncological patients and regression of skin aging[3,4].

Although vitamin A has been discovered and its importance has been understood in the last centuries, its toxicity has been known for thousands of years. In the studies on human fossils from ancient times, bone anomalies are thought to be caused by hypervitaminosis A[5,6].

Studies on vitamin A toxicity were primarily conducted to investigate the short-term acute effects in animals[7-9]. Intramuscular and intravenous forms of vitamin A were used in these studies. No significant data could be obtained from these studies since the gastrointestinal effects were bypassed[10,11].

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Increased nutritional and vitamin supplements in foods and increased interest in multivitamin supplements in developed countries have led to an increase in the level of vitamin A in the majority of the population[12]. Observational studies have shown that 75% of people receive vitamin A above the recommended daily intake[12]. Although vitamin A deficiency is a major health problem, particularly in developing countries, and public health entrepreneurs have drawn much attention to this problem, hypervitaminosis A, which has persisted throughout human history, may be an increasing but ignored problem.

Metabolism

People cannot synthesize vitamin A and therefore, meet their needs from the carotene in plants or foods of animal origin or supplements[13].

After its oral intake, vitamin A is absorbed by the epithelial cells in the small intestine, esterified and chylomicrons are formed with different fatty acids. Intestinal epithelial cells process chylomicrons or release them into circulation. Finally, chylomicron residues are either transported to target tissues or hydrolyzed in the liver and stored as retinol[14]. Retinol is then released into the circulation, binds to retinol-binding proteins, and enters the cell through the retinol-binding protein receptor in the target tissues[15]. Retinol is then processed to form palmitate and other retinyl esters in the cell or hydrolyzed with alcohol dehydrogenases in all tissues to form retinaldehyde. Retinaldehyde that is only present in the target cells is re-hydrolyzed through the enzyme dehydrogenase and retinoic acid is formed [16]. Retinoic acid shows its efficacy by interacting with the retinoic acid receptor (RAR) and retinoid X receptor (RXR) which are the members of the nuclear receptor family[17].

Toxicology

Daily vitamin A requirement is met from plants (provitamin A), meat and dairy products and medicines (preformed vitamin A). Seventy-five percent of the population in Europe, America, and other industrialized countries meet their daily vitamin A requirement from milk, butter, margarine, fish oil, or multivitamins that contain preformed vitamin A. Preformed vitamin A is absorbed by the intestines at the rates of 70–90%[18,19]. Developing countries meet their daily vitamin A requirements from plants in the form of provitamin A. The absorption rate of provitamin A by the intestines is 20–50% [20,21]. Vitamin A of plant origin (preformed vitamin A) toxicity is almost impossible due to the low absorption rate and difficult conversion into vitamin A[22-24].

Even if adults are exposed to vitamin A up to 100 times the recommended daily intake and children are exposed to vitamin A up to 20 times the recommended daily intake within hours or days, this exposure is not as problematic as a chronic toxicity. For this reason, acute vitamin A toxicity is quite uncommon[18,25].

Acute retinoid toxicity presents with mucocutaneous symptoms and laboratory findings. The most common mucocutaneous symptoms are dryness of the lips, cheilitis, and dryness of the oral, ophthalmic and nasal mucosa. Drying of mucous membranes is assumed to be due to reduced sebum production, thinning of epidermal thickness, and alteration of the epidermal barrier. Other cutaneous effects include general skin dryness, itching, peeling of palms and soles, and fissuring of fingertips. A significant amount of hair loss can be seen[26].

The most common side effect of topical retinoids is epidermal irritation. Temporary hypopigmentation, hyperpigmentation, psoriasis Koebner phenomenon, ectropion, and allergic contact dermatitis are among other side effects [26]. The peeling from topical retinoids is due to the hyperproliferation of the epidermis mediated by retinoic acid receptor stimulation[27].

Chronic toxicity develops after exposure to a large amount of preformed vitamin A for months or years. Daily intake of more than 25,000 IU for six years or more than 100,000 IU for six months is considered to be toxic. However, the lowest dose required to elicit toxicity cannot be calculated precisely because it varies from person to person[28-30]. The daily dose of 15,000 IU used in the treatment of degenerative eye diseases has been reported to be well tolerated after 12 years of treatment[31].

Children are more sensitive to vitamin A than adults. Daily intake of 1,500 IU/kg is reported to cause toxicity[28,29,32]. Similarly, elderly people are at risk for vitamin A toxicity compared to adults. Although the underlying cause of this increased risk is unknown, it is thought to be due to the increased intestinal absorption and chylomicron clearance of vitamin A[33,34].

The effect of genetic factors on intoxication is not known since the individual tolerances of vitamin A derivatives have not been adequately studied[18,29,35].

Many organs can be affected by chronic retinoid toxicity. Formation of bone spurs and bone resorption leading to calcinosis and hypercalcemia can be listed among its effects on bone[36]. Long-term consumption of high levels of vitamin A can stimulate bone resorption and may result in osteoporosis and hip fractures[37]. Central nervous system effects include

headache, nausea, and vomiting. Despite being rare, pseudotumor cerebri syndrome developed secondary to vitamin A has been reported[38]. Studies in which bexarotene was used in the treatment of cutaneous T-cell lymphoma have reported that reversible hypothyroidism has occurred upon discontinuation of treatment[39]. Furthermore, impairment was observed in reversible renal function tests during etretinate treatment[40].

Teratogenicity

Teratogenicity is the most worrying side effect in systemic retinoid use. Excessive intake of vitamin A has been associated with teratogenicity in both human and animal studies. Congenital malformation has been reported in 1 out of 57 pregnant women who were exposed to vitamin A intake greater than 10,000 IU/day via supplements[41]. Teratogenic findings include craniofacial (cleft lips/palates), cardiac (transposition of the great vessels), thymic and central nervous system (microcephaly, hydrocephalus) abnormalities[42]. Isotretinoin is estimated to increase the risk of malformation 25-fold. Vitamin A is thought to have a toxic effect on neural crest cells, possibly affecting the axial pattern regulation in the embryo through the Hoxb1 expression of the homeobox gene[43]. Animal and human studies have shown that the risk of teratogenicity from topical retinoids is quite low[44]. No minimum retinoid dose to be taken during pregnancy has been established yet.

Laboratory

The most common systemic effect of retinoids is hypertriglyceridemia. Both triglyceride and cholesterol levels have been shown to increase in patients taking bexarotene, isotretinoin, etretinate, and acitretin[45,46]. Acute hemorrhagic pancreatitis and eruptive xanthoma may develop secondary to hypertriglyceridemia.

High triglyceride and cholesterol levels are the most common laboratory abnormalities in patients receiving isotretinoin. These levels, therefore, should be checked periodically in patients receiving isotretinoin[47].

Although liver enzyme elevations are typically mild and reversible, alanine aminotransferase and aspartate aminotransferase enzymes are recommended to be monitored on a periodic basis in patients receiving treatment[26].

Furthermore, both urine and serum pregnancy (beta-hCG) tests are recommended in female patients twice 30 days before the initiation of isotretinoin treatment. Pregnancy should be monitored during treatment and up to 30 days after treatment[26].

Radiological imaging may be considered for hyperostosis in patients taking high-dose isotretinoin for a long time.

The presence of pseudotumor cerebri should be examined if the patient has a continuous complaint of headache during treatment.

Thyroid function tests should be monitored for hypothyroidism in patients taking bexarotene[48].

If the use of etretinate is required in patients with kidney disease, renal functions should be monitored during the course of treatment[40].

Treatment

For the reduction of skin irritation developed due to topical retinoid use, it is necessary to reduce the volume and frequency of the drug used and to use emollients.

Eye drops containing artificial tears and methylcellulose may be used for dryness of the eyes.

In cases where the triglyceride levels increase due to oral retinoid use, dose reduction or discontinuation of the drug may be considered due to the risk of pancreatitis if the triglyceride level is above 800 mg/dL. In cases where there is less increase, treatment can be continued by monitoring the course of triglyceride levels[26].

The combined use of a statin or fibrate is recommended due to the risk of pancreatitis after retinoid-induced hyperlipidemia in patients receiving bexarotene[49].

In cases where pseudotumor cerebri syndrome develops, discontinuation of vitamin A-containing medication and acetazolamide treatment have been found to be effective in reducing intracranial pressure[39].

Conclusion

Since vitamin A is essential for life, it has been added to most of the convenience foods in developed countries. Just as the harmful effects of vitamin A deficiency are known and necessary steps are taken with food and medicine supplements to eliminate this deficiency, so the presence of toxicity, as well as health and well-being, should be monitored in individuals exposed to high doses of vitamin A. Furthermore, the distribution and storage of vitamin A should be examined and genetic studies should be performed to determine individual tolerances in the face of increased hypervitaminosis A problem.

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Original Article

Eurasian Journal of Toxicology

Psychiatric Evaluation of Suicidal Drug Intake in the Emergency Department

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Abstract

Objective: Poisoning is usually caused by suicidal or unconscious intake of high doses of drugs or substances. Suicides are the voluntary termination of life, accounting for about 95% of all cases of intoxication, and are more common in female sex.

The aim of this study is to show the effects of psychiatric evaluations on the rates of re-admission and prognosis in emergency department admissions due to suicide attempt.

Materials and Methods: This was a retrospective study including patients over 18 years of age who were admitted to the Clinic of Emergency Medicine of University of University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey with suicide attempt due to intoxication or other reasons between 01.9.2018-01.09.2019. The patients were classified according to gender, exposure to the drug, and consultation with the psychiatrist. Approach to suicidal patients was also evaluated.

Results: Of the patients included in the study, 102 (56.98%) patients were consulted with psychiatrist and 16 (15.68%) of these patients had ongoing suicidal ideation. Of the patients with suicidal ideation, 9 (56.25%) were male;7 (43.75%) were female. 14 of the patients with suicidal ideation were admitted to the psychiatric service. 2 of them were admitted to the psychiatric service after medical treatment was completed in the internal medicine service. It was learned that 10 (5.58%) patients had previously attempted suicide. 9 (90%) were women; 1 (10%) was male. None of the 10 patients who had previously attempted suicide had reapplied.

Conclusion: Suicide; It is an issue that needs to be evaluated in detail with the thought, initiative and completion of the action. Patient admissions should be meticulously evaluated and, if any psychiatric illness should be diagnosed. Patients with no pathological findings and a decision to be discharged should be tried to avoid suicidal attempts.

Key words: Intoxication, Psychiatric evaluation, Suicide

Özet

Giriş: Zehirlenmeler genellikle intihar amaçlı veya bilinçsizce yüksek miktarda ilaç veya madde alımından kaynaklanır. İntihar, yaşamın gönüllü sonlandırılmasıdır, tüm zehirlenme vakalarının yaklaşık% 95'ini oluşturur ve kadın cinsiyetinde daha yaygındır.

Bu çalışmanın amacı intihar girişimi nedeniyle acil servis başvurularında psikiyatrik değerlendirmelerin yeniden başvuru ve prognoz oranları üzerine etkilerini göstermektir.

Gereç ve Yöntemler: Bu çalışma, 18 yaş üstü, Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi Acil Tıp Kliniğine, intoksikasyon veya başka nedenlere bağlı intihar girişimi ile başvuran hastaları kapsayan retrospektif bir çalışmadır. 01.9.2018-01.09.2019 tarihleri arasında, çalışma kriterlerini karşılayan hastalar cinsiyete, ilaca maruz kalmaya ve psikiyatriste danışmaya göre sınıflandırıldı. İntihar hastalarına yaklaşım da ayrıca değerlendirildi.

Bulgular: Çalışmaya alınan hastalardan 102'si (% 56.98) hpsikiyatriste danışılmış ve bu hastalardan 16'sında (% 15.68) intihar düşüncesinin devam ettiği görülmüştür. İntihar düşüncesi olan hastaların 9'u (% 56.25) erkekti, 7'si (% 43.75) kadındı. İntihar düşüncesi olan hastaların 14'ü psikiyatri servisine yatırıldı. Bunlardan 2'si dahiliye servisindeki tıbbi tedavisi tamamlandıktan sonra psikiyatri servisine yatırıldı. 10 (% 5.58) hastanın daha önce intihara teşebbüs ettiği öğrenildi. 9'u (% 90) kadındı; 1 (% 10) erkekti. Daha önce intihar girişiminde bulunan 10 hastadan hiçbiri tekrar başvurmamıştı.

Sonuç: İntihar, eylemin düşüncesi, girişimi ve tamamlanması ile ayrıntılı olarak değerlendirilmesi gereken bir konudur. Hastalar titizlikle değerlendirilmeli ve herhangi bir psikiyatrik hastalığı varsa teşhis edilmelidir.

Anahtar Sözcükler: İntihar, Psikiyatrik değerlendirme, Zehirlenme,

Introduction

The history of poison and poisoning dates back thousands of years. The word 'poison' is the first time in the literature that was defined as a drug and elixir prepared from deadly substances in B.C.1230[1]. Poisoning is usually caused by suicidal or unconscious intake of high doses of drugs or substances. Suicides are the voluntary termination of life, accounting for about 95% of all cases of intoxication, and are more common in female sex[2].

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It is known that the number of poisoning cases admitted to the emergency department in our country constitutes 0.46-1.57% of all cases[3,4]. Suicide attempts are frequently encountered in psychiatric patients. Sometimes there are suicide attempts in patients with undiagnosed psychiatric disorders. Most of the hospital admissions due to suicide are intoxications.

The aim of this study is to show the effects of psychiatric evaluations on the rates of re-admission and prognosis in emergency department admissions due to suicide attempt.

Materials and Methods

This was a retrospective study including patients over 18 years of age who were admitted to the Clinic of Emergency Medicine of University of University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey with suicide attempt due to intoxication or other reasons between 01.9.2018-01.09.2019.

The patients were classified according to gender, exposure to the drug, and consultation with the psychiatrist. Approach to suicidal patients was also evaluated.

The data obtained were analyzed using the using Statistical Package for the Social Sciences for Windows 25 (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to analyze the compliance to the normal distribution, and the chi-squareand t-tests were used for the remaining analyses. The quantitative data were expressed as mean, Standard deviation (SD) and median (minimum – maximum value), and the qualitative data were expressed as case number (n) and percentages (%). The outcomes were evaluated in 95% confidence interval and the significance was accepted at a level of $p<0.05$.

Results

The files of 186 patients admitted to our clinic were evaluated retrospectively. Patients whose investigation data were insufficient or who were recorded after unauthorized hospital leave were excluded from the study. Seven patients were excluded. 179 patients admitted to the emergency department for suicide were included in the study. Of the patients, 51 (28.5%) were male and 128 (71.5%) were female. The mean age was 32.7 years.

Among the patients included in the study, one (0.56%) patient was treated with suicide due to hanging and intoxication, one (0.56%) patient was treated with suicide due to incision; 177 (98.8%) patients were admitted with suicide only due to intoxication. One patient (0.56%) who presented with cardiac arrestdue to intoxication and substance intake was exitus.

29.2% [73] of the drugs taken for suicidal purposes could not be determined because the drug content could not be remembered by the patients and / or could not be found by their relatives or because the patient refused to declare the drug. All patients had multiple drug intake. Of the identified drug contents, 22% [55] were paracetamol, 21.2% [53] were NSAIDs (nonsteroidal anti-inflammatory drugs), 12.8% [32] were SSRIs (selective seratonin re-uptake inhibitors), %9.6[24] of them were antibiotics, 2.8% [7] were antihypertensive drugs, 1.6%[4] were aspirin and 0.8% [2] were TCA (tricyclic anti-depressant) (Figure.1).

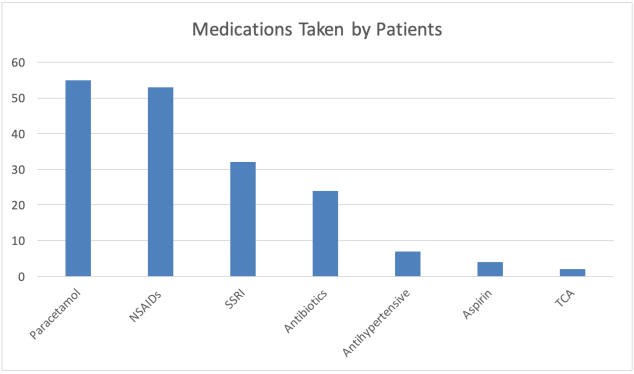

Figure 1. Medications Taken by Patients
NSAIDs, nonsteroidal anti-inflammatory drugs; SSRI, selective seratonin re-uptake inhibitors; TCA, tricyclic anti-depressant

Patients with a psychiatric illness; four (18.2%) patients had bipolar disorder, four (18.2%) patients had major depression, four (18.2%) patients had anxiety disorder, four (18.2%) patients had panic attacks, three (13.6%) patients had obsessive compulsive disorder, one patient (4.5%) had conversion disorder and one patient (4.5%) had substance addiction.

Of the patients included in the study, 102 (56.9%) patients were consulted with psychiatrist and 16 (15.7%) of these patients had ongoing suicidal ideation. Of the patients with suicidal ideation, nine (56.25%) were male; seven (43.75%) were female (Table 1).

14 of the patients with suicidal ideation were admitted to the psychiatric service. Two of them were admitted to the psychiatric service after medical treatment was completed in the internal medicine service. Of these 16 patients, two (12.5%) had major depression and two (12.5%) had bipolar affective disorder. The remaining 12 (75%) patients had no known psychiatric disease. Of the 102 patients consulted

Tablo 1. General Distribution According to Gender and Suicidal Ideation

	Psychiatrist Consultation-With Suicidal Ideation	Psychiatrist Consultation- No Suicidal Ideation	Patients not Consulted with Psychiatrists	Total
Male	9 (5%)	20 (11,2%)	22 (12,3%)	51 (28,5%)
Female	7 (3,9%)	66 (36,8%)	55 (30,7%)	128 (71,5%)
Total	16 (8,9%)	86 (48%)	77 (43%)	179 (100%)

with psychiatrist, 19 of them (18.6%) were admitted to the internal medicine service; 14 (13.7%) of them were admitted to the psychiatric service; four (3.9%) of them were taken to intensive care unit; two (1,96%) of them were admitted to the psychiatric service after the medical treatment was completed in the internal medicine service (Table 2).

It was learned that 10 (5.58%) patients had previously attempted suicide. Nine (90%) were women; one of them (10%) was male. None of the 10 patients who had previously attempted suicide had reapplied. Eight (80%) of these patients were consulted with psychiatrists. Of the patients consulted with psychiatrists, one (12.5%) had suicidal ideation and was admitted to the psychiatry service. Of the remaining seven patients, two patients (25%) were admitted to the internal medicine service; one patient (12.5%) was admitted to the intensive care unit. Of the patients included in the study, six patients (3.35%) had hospital admissions. Of these patients, three (50%) were male and three (50%) were female. It was seen that two (33.3%) of six patients who were re-admitted to hospital were consulted with psychiatrists. Two of these patients (33.3%) had suicidal ideation. One of these patients was admitted to the psychiatric service. Another patient was admitted to the internal medicine service and admitted to the psychiatric service after medical treatment. He was hospitalized in internal medicine and psychiatric service diagnosed as bipolar affective disorder.

Discussion

Poisoning occurs in adults mostly due to suicide attempts. Suicidal procedures applied to the hospital are mostly due to intoxication. Intoxications require a multidisciplinary approach and require psychiatrice valuation before discharge.

Three concepts were defined in the studies on suicidal behaviors. Completed Suicide: used for death-suicides. Suicide Attempt: This is done to attract attention or to draw attention to problems, as a result of which there is no death. Suicidal Ideation: The person has suicide plans[5,6,7].

It has been reported that climate, environmental characteristics and seasons have effects on suicide. There are also the types of suicide that Durkheim describes. These are selfish, irregular suicides and deadly suicides[5,8]. Beachler divides suicide types into escapism, aggression, dedication and game suicides. Shneidman's classification includes selfish, duplicated and abstraction suicides. Suicidal behavior varies between countries and societies. It is common in the Americans, Scandinavian countries and Central and Eastern Europe. It is rare in southern Europe. It is quite common in Japan. The difference in suicidal behavior between women and men decreases gradually. In both sexes, the 25-34 age group was the most suicidal group[5,9].

Suicide rates were; It increased to 1.95 per thousand in 1975, 1.69 per thousand in 1980, 2.42 per thousand in 1990, 2.67 per thousand in 2000 and 4.19 per thousand in 2013 [10].

Table 2. Hospitalization Rates of Patients Consulted with Psychiatrists

	Suicidal Ideation	No Suicidal Ideation	Total
Patients was admitted to the PS*	14 (%13,72)	-	14 (%13,72)
Patients was admitted to the PS after medical treatment in IMS**	2 (%1,96)	-	2 (%1,96)
Patients was admitted to the IMS	-	19 (%18,62)	19 (%18,62)
Patients was admitted to the ICU***	-	4 (%3,92)	4 (%3,92)
Discharged Patients	-	63 (%61,76)	63 (%61,76)
Total	1 6 (%15,68)	86 (%84,32)	102 (%100)

* psychiatric service **internal medicine service *** intensive care unit

Suicide is a problem of depression. Those with psychiatric disorders tend to have more depression than those without. However, patients can apply to the hospital with a suicide attempt before they are diagnosed with psychiatric disorder. In our study with 179 patients, only 22 patients had known psychiatric disorders. We think that this low rate is due to the lack of a psychiatric clinic in our hospital and the retrospective design of our study.

Although 10 of our patients had previous suicide attempts, there were no hospital admissions after the treatment in our hospital. This may be related to the lack of psychiatric services in our hospital.

Suicidal thinking is inherently dynamic. It is a dynamic variable in distinguishing the first suicide attempts from the first suicide attempts. Nonlinear dynamic models may provide advantages for suicide risk assessment and treatment monitoring in clinical settings[11]. In our study, 16 (15.7%) of 102 patients consulted with psychiatrist had suicidal ideation, and 14 of the patients with suicidal ideation were admitted to the psychiatric service. Two of them were admitted to the psychiatric service after medical treatment was completed. And only two (12.5%) of these 16 patients re-admitted. Of these 16 patients, two patients (12.5%) had major depression and two (12.5%) had bipolar affective disorder. The remaining 12 (75%) patients had no known psychiatric disease.

In conclusion, two of 22 patients with psychiatric disorders diagnosed with or without suicidal ideation underwent psychiatric hospitalization and two of them were admitted to the psychiatric service after medical treatment was completed. In a study examining suicide and survival, it was found that 19% of the patients who attempted suicide were admitted again with suicide attempt within two years, and poor adherence to treatment caused an increase in suicide risk[12]. In our study, none of the patients who had previously attempted suicide did not reapply during our study. Suicidal ideation was the main predictor of hospitalization or outpatient control.

Consultation with a psychiatrist is very important and the general clinical condition of the patient may be misleading. Four of the six patients who were re-admitted were not consulted with psychiatry. Two patients who were consulted had suicidal ideation and were admitted to the psychiatric service.

Suicide is more common in female gender worldwide[13]. Hospital admissions are more common in women due to toxic exposure other than suicide. In our study in which the demographic data of mushroom intoxications were examined, hospital admissions were higher in women (58.8%)[14]. In another study in which hospital application evaluations were made due to digoxin intoxication, hospital admissions were higher in women (67.8%). In addition, the rate of women in hospitalization was high (56.6%)[15]. Women are more likely to be exposed to verbal, emotional, economic and social violence than men[16].

In our study, paracetamol was the most common drug which are known among 29.7% of the patients. Paracetamol is commonly used for suicidal purposes because it is easy to access and cheap[17].

The rate of female patients in suicide attempts who applied to hospital was higher in our study (71.5%). The rate of female in the patients consulted with psychiatrist was high (40.8%). Only female patients with suicidal ideation after consultation were lower than male patients (3.9%).

Limitations

Although it is known that re-admissions are usually within 6 months, patients who applied within the last one year were included in our study. Therefore, the 6-month period of some patients remains unknown. Although we have been informed that the admission times are usually within the first two hours, the patient is likely to take medication or attempt a different suicide at different times.

Conclusion

Suicide; It is an issue that needs to be evaluated in detail with the thought, initiative and completion of the action. Patient admissions should be meticulously evaluated and, if any psychiatric illness should be diagnosed. Patients with no pathological findings and a decision to be discharged should be tried to avoid suicidal attempts. Further studies are needed, including suicide attempts that result in death.

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Original Article

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Retrospective Analysis of Geriatric Intoxication Cases

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Abstract

Objective: Physiology changing with age, comorbid diseases in the history of the patient and medication used for this reason cause the emergence of multiple complications in acute poisoning in geriatric age group. Chronic diseases basically present in this population are the most important cause of intentional toxic substance intake.

Materials and Methods: In this retrospective study, the data of patients aged 60 and older who referred to the Emergency Medicine Clinic of a tertiary Training and Research Hospital between 2009 and 2019 with a suspicion of intoxication were assessed through hospital information management system.

Results: 600 patients referred to emergency service for intoxication within a period of 10 years and 16 (2.66%) of these were in geriatric age group. The patients' age range differed between 60 and 85 years of age. In terms of age distribution, it was found that there were 3 (18.75%) patients aged 80 and older and 2 patients (12.5%) were found to ingest toxic substance intentionally. While male patients who were exposed to toxins unintentionally were higher in number (n=5, 31.5%), the number of patients who were exposed to toxins intentionally were higher among female patients (n=7, 43.75%). While the highest number of unintentional toxic substance exposure occurred with corrosive substance (n=7, 43.75%), the highest number of intentional exposure occurred by taking higher amounts of antipsychotic drugs (n=3, 18.75%) than the therapy dose prescribed for psychiatric diseases. 3 patients who were exposed to toxic substance intentionally were hospitalized and monitored and treated due to the characteristics of the toxic substances they were exposed to and since they had comorbid diseases.

Conclusion: Although intentional exposure to toxic substance is the dominant reason for acute intoxication in all age groups, unintentional exposure history is in the foreground in geriatric age groups. However, in 60 years of age and older population, situations which cause limitations in physical movement, depression, social isolation or the presence of diseases which are impossible to treat can cause the emergence of the feeling of self-destruction and result in suicidal attempt.

Key words: Geriatric, Intentional, Poisoning, Suicide, Unintentional

Özet

Giriş: Yaşla birlikte değişen fizyoloji, özgeçmişte bulunan komorbit hastalıklar ve bu nedenle kullanılan ilaçlar geriatrik yaş grubunda akut zehirlenmeler de çoklu komplikasyonların ortaya çıkmasına neden olur. Bu nüfusta temelde mevcut olan kronik hastalıklar istemli toksik madde alımlarının en sık nedenidir.

Materyal-Metod: Bu retrospektif çalışma, üçüncü basamak Eğitim ve Araştırma Hastanesinin Acil Tıp Kliniğine 2009 ve 2019 yılları arasında zehirlenme şüphesi nedeniyle başvuran 60 yaş ve üzeri geriatrik hastaların verileri, hastane bilgi yönetim sistemi üzerinden değerlendirildi.

Bulgular: 10 yıllık süre içerisinde zehirlenme nedeniyle acil servise 600 hasta başvurmuş, bunlardan 16'sı (%2.66) geriatrik yaş grubuna aitti. Hastaların yaş aralığı 60 ve 85 yaş arasında değişmekteydi. Yaşa göre dağılıma bakıldığında 80 yaş ve üzerinde 3 hastanın (%18.75) olduğu ve 2 hastanın (%12.5) istemli olarak toksik madde alımı olduğu tespit edildi. İstemeden toksine maruz kalan hastalarda erkek cinsiyet (n=5, %31.5) daha fazlayken isteyerek kasıtlı olarak maruz kalan hastalarda kadın cinsiyet (n=7, %43.75) sayıca fazlaydı. İstemeden toksine maruz kalan hastalarda en fazla koroziv maddeye (n=7, %43.75) maruziyet varken isteyerek kasıtlı olarak maruziyette ise hastaların psikiyatrik hastalıkları nedeniyle aldıkları antipsikotik ilaçların (n=3, %18.75) tedavi dozundan daha yüksek miktarlarda alımı vardı. İsteyerek kasıtlı olarak toksik maddeye maruz kalan 3 hasta, aldıkları toksik maddelerin özellikleri ve ek komorbit hastalıkları olması nedeniyle yatırılarak takip ve tedavileri yapılmış.

Tartışma: İstemli olarak toksik maddeye maruziyet tüm yaş gruplarında akut zehirlenmenin baskın nedeniyken geriatrik yaş gruplarında istemsiz maruziyet öyküsü ön plandadır. Ancak 60 yaş ve üzeri nüfusta fiziksel hareket kısıtlılığına neden olan durumlar, depresyon, sosyal izolasyon ya da tedavisi mümkün olmayan hastalıkların varlığı kendi kendine zarar verme duygusunu ortaya çıkartarak intihar girişimine neden olabilmektedir.

Anahtar Sözcükler: Geriatrik, İstemli, İstemsiz, Öz kıyım, Zehirlenme

Introduction

In addition to being an important health problem in all societies, poisoning is also a sociocultural and economic burden[1, 2]. Both intentional and unintentional toxic substance exposure is the reason for acute poisoning in geriatric age groups of 60 years and older. Geriatric group constitutes about 2,3% and 5,3% of all the patients who refer with acute intoxication[3]. In addition, comorbid diseases in the history of this age group, the medication used for this reason and

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the physiological structure that changes with age prepare a basis for the emergence of multiple complications caused by toxicity[4].

Chronic illnesses, psychiatric background and/or diseases are seen as the most important reason for toxic substance exposure in old patients. Studies conducted have reported that old age is a reason for suicide in many parts of the world and that this risk is higher in individuals aged 65 and older when compared with the young population[5, 6].

The aim of this study is prospective assessment of 60 years of age and older patient group who referred to a tertiary healthcare hospital for acute poisoning.

Materials and Methods

This retrospective study was conducted in the Emergency Medicine Clinic of a tertiary Training and Research Hospital between 2009 and 2019. The data of 60 years of age and older patients who referred with a suspicion of poisoning were collected through hospital information management system. The patients were grouped in two categories as unintentional and intentional toxin exposure according to ICD 10 codes. The two groups were compared in terms of demographic parameters, clinical findings, symptoms, complications and mortality/morbidity.

The toxin was determined through files according to anamnesis taken from the patient, family or relatives. The detailed history of the underlying comorbidity, predisposition of the psychiatric conditions which triggered the suicide attempts and the underlying situations were assessed in all patients.

The toxic agents taken were classified as corrosive substance, selective serotonin reuptake inhibitors (SSRI), organophosphate, antipsychotic, nonsteroid anti-inflammatory drug, antiepileptic, rat poison, and toxic alcohol intoxication.

The data were assessed by using SPSS for Windows version 17 (SPSS, Chicago, IL, United States). Descriptive statistics were given as average ± standard deviation for metrical discrete variables and as case and percentage number for categorical variables.

Results

It was found that 600 patients referred for intoxication within a period of 10 years and 16 (2.66%) of these were in geriatric age group. In terms of age distribution, it was found that there were 3 (18.75%) patients aged 80 and older and of these three patients, one patient (6.25%) was found to have involuntary exposure, while 2 (12.5%) were found to be exposed to toxic substance intentionally. Demographic characteristics of the patients are summarized in Table 1.

Table 1. Demographic characteristics of geriatric patients who referred for poisoning (n=16).

Female		10 (62.5%)
Male		6 (37.5%)
Age		67.25 ±8.5 (min.:60, max.:85)
Unintentional exposure		8 (50%)
Intentional exposure		8 (50%)
Psychiatric disease history	Unintentional exposure	1 (6.25%)
	Intentional exposure	3 (18.75%)

While male patients who were exposed to toxins unintentionally were higher in number (n=5, 31.5%), the number of patients who were exposed to toxins intentionally were higher among female patients (n=7, 43.75%). Psychiatric disease history was in the forefront in female patients n=4, 25%)

While the highest number of unintentional toxic substance exposure occurred with corrosive substance (n=7, 43.75%), the highest number of intentional exposure occurred by taking higher amounts of antipsychotic drugs (n=3, 18.75%) than the therapy dose prescribed for psychiatric diseases. Frequency of toxic subtance is shown in Table 2.

The most frequent reason for referral following corrosive substance intake was burning sensation in the throat (n=7, 43.75%). In the physical examination following referral, hyperemia was seen in pharynx region in 4 patients (25%) and in the emergency endoscopic assessment, while esophagitis due to corrosive substance was found in 3 patients (18.75%), hemorrhage and ulceration findings due to transmural involvement were found in one patient (6.25%). Since no pathologies were found in the symptoms and phys-

Table 2. Toxic substances patients were exposed to

Unintentional exposure	Corrosive substance	7 (43.75%)
	Toxic alcohol	1 (6.25%)
Intentional exposure	Antipsychotic	3 (18.75%)
	NSEID	2 (12.5%)
	Antiepileptic	1 (6.25%)
	Anxiolytic	1 (6.25%)
	Rat poison	1 (6.25%)

ical examinations of 3 patients who referred following corrosive substance ingestion, they were discharged following 4-hour-long emergency service follow-up as a result of not developing intolerance to solid and liquid food. However, 3 (18.75%) of the patients who were found to have symptoms and pathological findings in physical and endoscopic examination were followed for 24 hours in clinic and discharged with the recommendation of control. The patient who was found to have transmural hemorrhage and ulceration in endoscopic assessment was followed-up in the intensive care unit and became exitus on the third day of follow-up after developing mediastinitis.

The patient who was exposed to toxic alcohol unintentionally was brought to emergency service by his relatives for blindness and sleeping state. He was hospitalized and treated in the intensive care unit after increased anion-sparing metabolic acidosis and renal failure was found in his assessment. Three patients who were exposed to toxic substance intentionally were hospitalized and treated because of the characteristics of the toxic substances they ingested and since they had comorbid diseases. Among this patient group, the patient who had a history of schizophrenia diagnosis and who was poisoned due to toxic dose intake of the drug called Lityum that he was using was followed in the intensive care unit. When the intentional toxic substance intake group was examined generally, it was found that 8 (50%) patients had a chronic disease that could cause comorbidity and they took these substances to get rid of the chronic picture caused by these diseases

.

Discussion

With the decrease in fertility and deaths, an increase in old population has occurred. This increase has also caused an increase in the incidence of chronic diseases, disabling diseases and diseases causing stress. Thus, both intentional and unintentional toxic substance exposures that we see in young population also began to be seen in old population[7]. In this study, when age distribution was reviewed, it was found that 18.75% of the patients were 80 years old and older. When the characteristics of this patient group were examined, it was found that 12.5% were exposed to toxic substance intentionally due to their chronic diseases affecting quality of life. The results of studies conducted are in parallel with our results in this aspect[8].

There are not many studies about the clinical features of acute poisoning in geriatric age group. While it was found in previous acute poisoning cases that male gender was on the forefront[3], females were on the forefront in the present study. It is thought to result from the differences of fighting social differences and the pressures on the female gender in our region. However, while there were more males involved in unintentional exposures, there were more females involved in intentional toxic substance exposure.

While intentional toxic substance exposure is the dominant reason of acute poisoning in all age groups, geriatric age group has unintentional exposure history[9]. In our study, the rates of intentional and unintentional exposure to toxic substance were found to be equal. The characteristics of the toxic substance patients were exposed to show social and even regional differences. For example, irrespective of general age and gender, the toxic substance most exposed to in society is drugs with a rate of 56% in Iran, while its is corrosive substances used at home in India with 44% [10, 11].

Chemical substances used at home are sources of intentional or unintentional exposure in different age groups[12]. The rate of mortality is higher especially in exposures of individuals aged 60 and older when compared with other age groups. While complications of the respiratory system are seen as the reason for increased mortality, no association was found between gastrointestional system complications and mortality[13]. Mediastinitis developed in one patient and resulted in death in the present study. Lesions were found in 18.75% of the patients in endoscopic assessments of the gastrointestional system; however, the patients were discharged from the emergency service without developing any complications as a result of follow-ups. This result is also in parallel with the literature.

As in young population, 60 years and older age group also consume alcohol[14]. Old individuals may consume it as a response to severe life conditions. Studies conducted have not found differences in terms of both complications and intensive care follow-up durations of this patient group following toxic alcohol intake[9]. In the present study, toxic alcohol intake was found in one patient and the patient was not found to differ with the group younger than 60 years of age in terms of the clinical picture that emerged in the follow-ups.

For geriatric population, the toxic substance most exposed to was found to be drugs[14]. In our study, it was found that the substances taken intentionally for self-harm were drugs the patients were using for their existing psychiatric diseases or chronic diseases. In the population aged 60 and older, situations which cause limitations in physical movement, depression, social isolation or the presence of diseases which are impossible to treat can cause the emergence of the feeling of self-destruction and result in suicidal attempts[15]. In the present study, of the patients who were exposed to toxic substance intentionally, 18.75% had a psychiatric dis-

ease, 18.25% had diseases such as cancer and chronic cardiac failure that they thought could not be treated and 6.25% had a condition that caused limitation of motion. These results, especially the positive association between underlying diseases and the structural, physiological and psychogenic changes caused by these diseases were in parallel with other results conducted[14, 15].

Globally, pesticides are considered to be responsible for 30% of intentional toxic substance exposures. In our country, as in countries such as China, Africa and India, pesticides are the most ingested toxic substances for suicidal purposes between 16 and 60 years of age and rodenticides are the second most ingested substances according to the data of National Poison Information Centre[16]. One of the patients in this study was older than 80 years of age and she stated that she ingested rat poison to get rid of the situation she was in due to ovarian cancer. This situation is a result of desperation in geriatric population and it occurs as an indicator of the wish of individuals to end their lives.

Mortality rates which occur as a result of toxic substance exposure are determined by the toxic substance exposed to, age and comorbid diseases. In patients aged 60 and older, the rates differ based on country and region[17, 18]. However, the important point here is being aware of the fact that a population with a high risk is in question rather than mortality rates and more care should be taken in emergency service management of the patients.

Not many studies were found in literature about the exposure of 60 years of age and older population with intentional and unintentional toxic substance. Although 10-year-long patient data were assessed in the present study, the most important reasons for limitation are the fact that the study had a single centre and the number of cases was low. However, the reasons for the low number of cases in the study are thought to be the fact that intentional self-harm is not considered as a suitable behaviour in terms of religion and morality in the society the study was conducted in and that the age group was 60 years of age and older.

As a conclusion, geriatric patient group show a higher tendency to undesired drug reactions or unintentional poisoning as a result of multiple drug use and getting unprescribed drugs. Together with natural physiological changes associated with aging, altered pharmacological and pharmacokinetic characteristics create a tendency for this situation. This is the reason why there are more complications when compared with young patient population. Starting the treatment to detect toxic exposure on time and to prevent the development of multiple complications and treatment management should be the job of emergency physician. Necessary social support programs should be support by knowing that there is a high toxic substance exposure risk especially in geriatric population. In case of determination of destructive reasons such as psychiatric, chronic and sociodemographic diseases, treatment can be possible only through assessment of many disciplines such as emergency medicine, psychiatry and family practice within an integrated approach.

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Original Article

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2012-2019 Yılları Arasında Acil Servise Parasetamol İntoksikasyonu ile Başvuran Hastaların Retrospektif Analizi

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Abstract

Objective: This study was planned to analyze some variables such as demographic, clinical, treatment, side effects, laboratory data of patients taking paracetamol for self-harm in a tertiary emergency department.

Materials and Methods: This is a retrospective study. Patients over 18 years of age who received paracetamol active substance for suicidal purposes in the emergency department of Atatürk University Research Hospital between 14.01.2012 and 04.05.2019 were included in the study. Patients with chronic disease, pregnant women, patients with poor general condition and missing data were excluded from the study.

Results: 129 patients were included in the study. 89 (69%) of the patients were female. The mean age of the patients was 25.8 ± 8.6 years. The ages of the patients ranged from 18 to 69 years. Forty-three patients had received paracetamol in toxic doses. There was a correlation between the amount of paracetamol and blood paracetamol levels. There was no significant relationship between the amount of paracetamol and other blood parameters.

Conclusion: In our study, there was a correlation between the amount of paracetamol taken and blood paracetamol level. However, there was no statistically significant difference in liver function tests and International Normalized Ratio (INR) values. Further prospective studies are needed.

Key words: Acetaminophen, INR, Intoxication, Liver function tests, Paracetamol

Özet

Giriş: Bu çalışma üçüncü basamak bir acil servis kliniğine kendine zarar verme amacıyla parasetamol alan hastaların demografik, klinik, tedavi, yan etkiler, laboratuar verileri gibi bir takım değişkenlerin analizini yapmak amacıyla planlanmıştır.

Materyal-Metod: Bu çalışma retrospektif bir çalışmadır. Çalışmamıza 14.01.2012 ile 04.05.2019 tarihleri arasında Atatürk Üniversitesi Araştırma Hastanesi acil servis polikliniğine suisiid amacıyla parasetamol etken maddeli ilaç alan 18 yaş üstü hastalar dahil edildi. Veriler hasta dosyaları taranarak elde edildi. Kronik hastalığı olanlar, gebeler, genel durumu kötü olanlar, eksik verisi olanlar çalışma dışı bırakıldı.

Bulgular: Çalışmamıza 129 hasta dahil edildi. Hastaların 89'u (%69) kadın cinsiyetteydi. Hastaların yaş ortalaması 25,8 ± 8,6'ydı. Hastaların yaşları 18-69 arasında değişmekteydi. 43 hasta toksik dozda parasetamol almıştı. Hastaların aldıkları parasetamol miktarı ile kan parasetamol düzeyi arasında korelasyon vardı. Alınan parasetamol miktarı ile diğer kan parametreleri arasında anlamlı ilişki yoktu.

Tartışma: Çalışmamızda alınan parasetamol miktarı ile kan parasetamol düzeyi arasında korelasyon tespit edilmiştir. Ancak karaciğer fonksiyon testlerinde ve Uluslararası Düzeltme Oranı (INR) değerinde istatistiksel olarak anlamlı bir farklılık gösterilememiştir. Bu konuda daha fazla prospektif çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Asetaminofen, INR, İntoksikasyon, Karaciğer fonksiyon testleri, Parasetamol, Zehirlenme

Giriş

Asetaminofen 1955 'den beri ABD'de en sık kullanılan ağrı kesici-ateş düşürücüdür. Dünya genelinde yüzlerce ilaç içeriğinde kombine olarak bulunur[1]. Asetaminofen (parasetamol) doz aşımı kazara veya kasıtlı olarak aşırı dozda ilaç alımı sonucu ortaya çıkar ve acil servis başvuruları arasında önemli bir yer tutar. Parasetamol, dünya çapında özellikle gençler arasında öz kıyım için en sık kullanılan ilaçtır. Bu durumun muhtemel sebebi ilaca ulaşmanın nispeten kolay olmasıdır. İngiltere'de her yıl yaklaşık 98.000 hasta parasetamol zehirlenmesiyle acil servislere başvurmakta ve yaklaşık 49.000 hasta hastaneye yatarak tedavi edilmektedir. Yalnızca parasetamol zehirlenmesine bağlı İngiltere'de her yıl tahminen 150 - 200 ölüm ve 15 - 20 karaciğer nakli gerçekleşmektedir[2,3,4].

Parasetamolün 75 mg / kg'dan daha az alımlarının hepatotoksisiteye yol açma ihtimali düşüktür. Bununla birlikte, terapötik dozlarda hepatotoksisite vakaları bildirilmiştir. Parasetamol doz aşımından kaynaklanan ölüm oranı yaklaşık

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% 0,4'tür, ancak tedavi olmayan birçok hastada kan parasetamol düzeyine bağlı olarak ciddi karaciğer hasarı meydana gelir[3].

Parasetamol'un terapötik serum konsantrasyonları 10-20 mcg/mL (65-130 mikromol / L) arasındadır[5]. Tek seferde 7,5-10 gram asetaminofen alınması ise toksik doz olarak tanımlanır[6]. Toksisitenin 200 mg/kg'dan daha yüksek tek dozda veya 24 saatlik bir süre zarfında 10 gramdan daha yüksek alımlarda ortaya çıkması olasıdır. 350 mg/kg'ı aşan dozlarda uygun tedavi edilmedikçe neredeyse tüm hastalarda ciddi karaciğer toksisitesi gelişir[7]. Tek seferde çocukta 150 mg / kg'dan daha az veya yetişkinde 7,5 - 10 gramdan az alımlarda toksisite gelişmesi beklenmez[8]. Eliminasyon yarı ömürleri, tüm asetaminofen preparatları için iki ila dört saat arasındadır, ancak eliminasyon fazı, uzun tablet erimesi ve emilimine bağlı olarak uzatılmış salınımlı preparatlar için başlangıçta uzayabilir[9,10].

Parasetamol zehirlenmesinin ilk tanımlandığı yıllara göre günümüzde karaciğer yetmezliği ve ölüm vakaları daha az görülmektedir. Nispeten düşük ölüm sayısının temel nedeni, 1970'lerden bu yana intravenöz veya oral olarak uygulanan oldukça etkili bir antidot olan N asetil-sisteinin (NAC) kullanılmasıdır.

Asetilsistein oral veya % 5 dekstroz içinde intravenöz olarak verilebilir. Antidot tedavisine temelde alınan doza ve nomograma göre başlanır. N asetil-sisteinin tedavisinde, yan etki olarak özellikle bulantı-kusma ve anafilaktoid reaksiyonlar sık görülmektedir[11].

Bu çalışma ile kliniğimize öz kıyım amacıyla parasetamol içeren preperatları alan hastaların demografik özellikleri ve tedavi rejimleri araştırılarak, literatüre katkı sağlanmak istenmiştir.

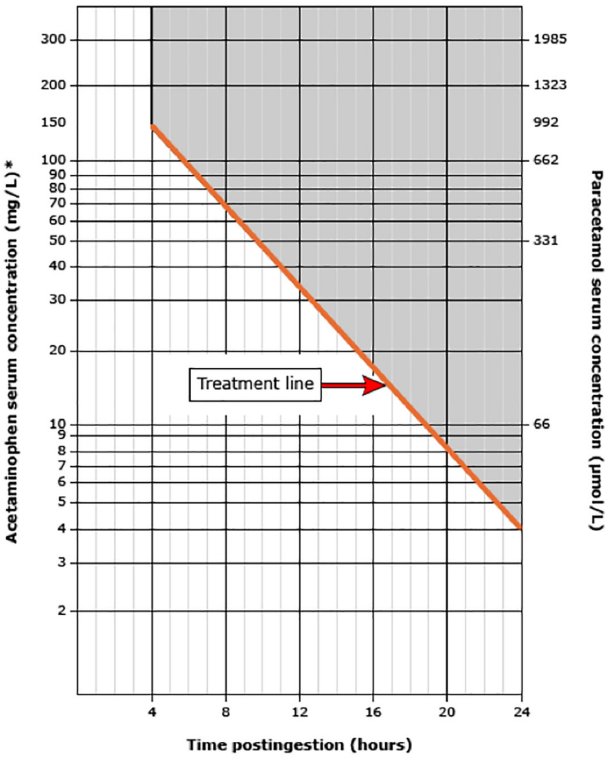
Gereç ve Yöntem

Bu çalışma retrospektif olarak tasarlanmıştır. Çalışmamıza 14.01.2012 ile 04.05.2019 tarihleri arasında Atatürk Üniversitesi Araştırma Hastanesi acil servis polikliniğine öz kıyım amacıyla parasetamol etken maddeli ilaç alan 18 yaş üstü hastalar dahil edildi. Veriler hasta dosyaları taranarak elde edildi. Kronik hastalığı olanlar, gebeler, genel durumu kötü olanlar, eksik verisi olanlar çalışma dışı bırakıldı.

Hastaların yaşı, cinsiyeti, vital bulguları, aldıkları etken maddeler ve ne kadar aldıkları, parasetamole ek ilaç alıp almadıkları, aldıkları parasetamol miktarı, acil serviste NAC tedavisi yapılıp yapılmadığı, mide lavajı ve aktif kömür uygulanıp uygulanmadığı, dış merkezden sevk durumu, dış merkezde mide lavajı ve aktif kömür uygulanıp uygulanmadığı, başvuru esnasında kan parasetamol düzeyi, başvuru anından itibaren 48 saat boyunca aralıklarla yapılan laboratuvar tetkik sonuçları kaydedildi.

Tek seferde 200 mg/kg'ın veya 10 gramdan fazla alım, 24 saat içinde 10 gram ya da 200 mg/kg'dan fazla, ardışık 2 gün boyunca günde 6 gram veya 150 mg/kg'dan fazla alımlar toksik doz olarak kabul edildi.

Kliniğimizde hastalara NAC tedavisi hastanın toksik dozda parasetamol alıp almadığı ve Rumack Matthew nomogramına (Şekil 1) göre tedavi gereksinimi olup olmadığı göz önüne alınarak başlanmaktadır.



Şekil 1. Rumack-Matthew Parasetamol Nomogramı[5]

İstatistiksel Analiz

İstatistiksel analiz IBM spss 20 programı kullanılarak yapıldı. Kesikli ve sürekli sayısal değişkenlerin dağılımının normal dağılıma uygun olup olmadığı Kolmogorov Smirnov testi ile belirlendi. Tanımlayıcı istatistikler kesikli ve sürekli sayısal değişkenler için median (minimum-maksimum), kantitatif veriler görülme sayısı ve yüzde (%) olarak verildi. Non-parametrik bağımsız değişkenler kıyaslanırken Mann-Whitney U testi kullanıldı. Normal dağılmayan değişkenler arasında korelasyon olup olmadığı Pearson korelasyon testi ile değerlendirildi. $p<0,05$ istatistiksel anlamlılık eşik değeri olarak alındı.

Bulgular

Çalışmamızda yedi yıl boyunca acil servis polikliniğine ilaç intoksikasyonu nedeniyle başvuran 1871 hastanın dosyası incelendi. Bu hastalarında 162'sinin parasetamol aldığı

tespit edildi. 19 hasta eksik veri nedeniyle, 9 hasta gebelik nedeniyle, 5 hasta kronik hastalıkları nedeniyle çalışma dışı bırakıldı. Çalışmaya nihai olarak 129 hasta dahil edildi.

Hastaların 40'ı (%31) erkek, 89'u (%69) kadındı. Hastaların yaş ortalaması 25,84 ± 8,6'ydı. Hastaların yaşları 18-69 arası değişmekteydi. 43 hasta toksik dozda parasetamol almıştı. 21 hastada dördüncü saat parasetamol düzeyi tedavi verilmesi gereken düzeyin üzerindeydi. Hastaların 76'sına (%58) NAC tedavisi uygulanmıştı. Toksik dozda alımı olan veya dördüncü saat parasetamol düzeyi 150 mikrogram/ml üzerinde olan tüm hastalar intravenöz (iv) NAC tedavisi almıştı. N-Astetil-Sistein tedavisi alan hiçbir hastada alerjik veya anaflaktoid reaksiyon kaydedilmemişti. Hastaların 116'sına (%89) mide lavajı uygulanmıştı. Mide lavajı uygulanan hastaların %66'sına merkezimizde geri kalanına ilk başvurulan merkezde lavaj işlemi yapılmıştı. Hastaların 81 tanesine (%62) merkezimizde aktif kömür uygulanmıştı (Tablo 1).

Hastaların aldıkları parasetamol miktarı ile kan parasetamol düzeyi arasında pozitif yönde korelasyon vardı. Parasetamol düzeyi ve alınan parasetamol miktarı ile diğer kan parametreleri arasında ise başvuru anında ve takip eden 48 saat içerisinde korelasyon yoktu.

Kadınlar ve erkekler arasında alınan parasetamol miktarı ve kan parasetamol düzeyleri açısından anlamlı fark yoktu. (p:0,880, p:0,104). Ayrıca veriler incelendiğinde karaciğer fonksiyon testleri ve International Normalized Ratio (INR) değerleri ile NAC tedavisi verilmesi arasında bir ilişki yoktu (p:0,710, p:0,740, p:0,214).

Ayrıca NAC tedavisi uygulanan hastaların hiçbirinde anafilaksi gelişmezken birkaç hastada geçici mide bulantısı veya baş ağrısı görüldü. Ancak NAC tedavisine devam edildi.

Tartışma

Asetaminofen'in yaygın tıbbi kullanımına 1947'de başlandı. İlk zamanlarda ABD'de, asetaminofen sadece reçete ile satılmaktaydı. 1960 yılında, preparat tezgah üstü (OTC) durumuna geçti. OTC preparatlarında asetaminofen mevcudiyeti hem pediatrik çağ hem de erişkinler için asetaminofeni tüm dünyada en sık kullanılan ağrı kesici-ateş düşürücü konumuna getirdi.

Parasetamol (ABD ve Kanada dışında) olarak da bilinen ve kimyasal adı *N* -asetil-p-aminofenol (APAP) Asetaminofen, tek bir ajan olarak veya kombinasyon halinde yüzlerce ilacın içinde mevcuttur.

Parasetamol toksisitesi nispeten sık görülür. Parasetamol, uygun terapötik dozlarda uygulandığında güvenli bir ajan olsa da, yanlış kullanım ve aşırı dozda hepatotoksisite ortaya çıkabilir.

Parasetamol toksisitesi çocuklarda yaygın olmakla birlikte, ciddi ve ölümcül vakaların çoğunu yetişkinler oluşturur. Parasetamol toksisitesi, Birleşik Krallık'ta karaciğer transplantasyonu gerektiren hepatik yetmezliğin en yaygın nedenidir. ABD'de, parasetamol toksisitesi, transplantasyon gerektiren en sık ikinci karaciğer yetmezliği nedenidir[12]. Bizim çalışmamıza dahil edilen hastaların tamamı kendine zarar verme amacıyla parasetamol almıştı. Yalnızca üç hastada ciddi karaciğer yetmezliği düşündürecek karaciğer enzim yüksekliği tespit edildi. Hastaların hiçbirinde nakil ihtiyacı olmadı.

Yetişkinler için günlük terapötik maksimum parasetamol dozu 4 g'dır. Klasik kullanım 4-6 saatte bir 325-650 mg veya 6 saatte bir 1 g şeklindedir. 12 yaşından küçük ve/veya 50 kg'dan hafif çocuklar için, maksimum günlük doz 75 mg/kg'dır[13]. Bizim çalışmamızda hastaların çoğu terapötik doz aralığında, hastaların %33'ü de toksik dozda parasetamol almıştı.

Parasetamol zehirlenmelerinde çoğu hasta başlangıçta asemptomatiktir. Ancak olası bir karaciğer yetmezliğinin bulguları 24-48 saat içinde görülebilir[13,14]. Isbister ve arkadaşlarının 654 hasta ile yaptıkları çalışmada hastaların yaş ortancasının 29 (18-98), 453 hastanın kadın cinsiyette olduğu tespit edilmiştir. Yine bu çalışmada NAC alan hastaların %33'ünde

Tablo 1. Temel İstatistik Verileri.

	Görülme Sayısı veya Ortalama	Görülme Yüzdesi veya Minimum-Maksimum Değer
Kadın	89	%69
Yaş ortalaması	25,8 ± 8,6	(Min:18-Max:69)
Toksik dozda ilaç alanlar	43	%33
N-Astetil-Sistein uygulaması	76	%58
Mide lavajı uygulaması	116	% 89
Aktif kömür uygulaması	81	%62
4. saat parasetamol pozitif hasta	21	%16
Alınan parasetamol (gram)	7,53 ±5,96	(Min: 0,3 – max: 40)
Sistolik Tansiyon Arteriyal (mmHg)	123,3 ±13,76	(Min:73-Max:163)
Diastolik Tansiyon Arteriyal (mmHg)	73,6 ± 10,36	(Min:43-Max:100)
Nabız (/dk)	82,8 ±15,72 /dk	(Min:43-Max:129)

çeşitli yan etkiler 3 tanesinde ise ciddi anafilaksi görüldüğü bildirilmiştir[15]. Başka bir çalışmada vakaların %71'inin kadın cinsiyette olduğu görülmüştür[16]. Bizim çalışmamızda NAC'a bağlı anafilaksi görülmedi. Çalışmamızda hastaların yaş ortalaması 25,8 ± 8,6 olarak bulundu. Ayrıca çalışmamızda tespit ettiğimiz cinsiyet verileri de literatür ile uyumludur.

Gunnell ve arkadaşları, parasetamol zehirlenmesinden kaynaklanan ölüm oranlarının Birleşik Krallık'ta Fransa'ya kıyasla dört kat daha yüksek olduğunu tespit etmişlerdir. Bunun nedeninin Fransa'da mevzuatın parasetamol paketlerini 8 gram ile sınırlı tutması olduğunu bildirmişlerdir[17]. Ülkemizde tek pakette 10-13 g parasetamol bulunabilmektedir. Bizim çalışmamızda ise ölümle sonuçlanan vaka görülmedi.

Read ve arkadaşları yaptıkları çalışmada alındığı iddia edilen parasetamol miktarını, 4 ila 60 gram arasında olduğunu, hastaların çoğunun 25-50 gram arasında ilaç aldığını bildirmişlerdir. Anamnezde belirtilen parasetamol dozu ile serum parasetamol konsantrasyonları arasında korelasyon bulunamamıştır[18]. Bizim çalışmamızda ifade edilen parasetamol düzeyi ile kan parasetamol konsantrasyonları arasında korelasyon tespit edildi. Ayrıca çalışmamızda alınan parasetamol miktarları 3-40 gram arasında değişmekteydi.

Bir başka çalışmada, 95668 hasta çalışmaya dahil edilmiş, 2007-2017 yılları arasında yıllara göre hem vaka sayısının hem de hepatotoksisite gelişen hasta sayısının arttığı tespit edilmiştir. Bizim çalışmamızda da benzer şekilde her yıl vaka sayısının artmış olduğu görüldü. Bu artış istatistiki olarak anlamlı değildi. Bu durumun çalışmanın retrospektif olması ve geçmiş yıllara ait verilerin eksikliğinden kaynaklanma ihtimali yüksektir. Bu bilgi de bizim çalışmamız ile uyumludur[19].

Yapılan başka bir çalışmada INR değerinin karaciğer yetmezliğinden bağımsız olarak yüksek olabileceği belirtilmiştir[20]. Bizim çalışmamızda INR değerinde anlamlı bir yükseklik tespit edilmedi. Yapılan bir başka çalışmada altı karaciğer nakli vakası incelenmiş bunların üç tanesinin akut parasetamol zehirlenmesne bağlı geliştiği gösterilmiştir[21]. Bizim çalışmamızda ise hiçbir hasta karaciğer nakline ihtiyaç duymamıştır.

Sonuç

Çalışmamızda alınan parasetamol miktarı ile kan parasetamol düzeyi arasında korelasyon tespit edilmiştir. Ancak karaciğer fonksiyon testlerinde ve INR değerinde istatistiksel olarak anlamlı bir farklılık gösterilememiştir. Parasetamol zehirlenmesi ile ilgili yapılan çalışmaların büyük çoğunluğu ulusal zehir kayıt merkezleri veya hastane verilerine dayanarak yapılan retrospektif çalışmalardır. Ancak bu yöntemde eksik verilerin varlığı çalışmaların çıktılarını önemli ölçüde değiştirebilmektedir. Bu nedenle parasetamol zehirlenmeleri konusunda yapılacak prospektif çalışmalar literatüre daha fazla katkı sağlayacaktır.

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Original Article
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İlaç Alımına Bağlı Zehirlenmelerin Analizi

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Abstract

Objective: Drug intoxications are one of the most reasons to applications for emergency department and hospitalizations at intensive care units. Especially multiple drug uses are unpredictable threat for mortality and morbidity.

Materials and Methods: In our study, we evaluate retrospectively for blood parameters, hospitalization time and some personalinformation about the patients who came to our emergency service for toxication after using multiple drugs. We examined the relationship between the blood pH, lactat, white blood cells, hemoglobin, platelets, alanine aminotransferase and aspartate aminotransferase levels of the patients when their applications in emergency department and patients length of hospital stay or intensive care unit stay, discharge and mortality. The patients' hospitalization information are giving in the research.

Results: 80 patients are being included in this research. 47 of them stayed at service units, 23 of them stayed at intensive care units, 4 of them discharged from the emergency department and 6 of them left the research without permission. There was no significant correlation between the blood parameters in the hospital administration and the state of hospitalization.

Conclusion: In our research, the intensive care unit hospitalization found more than the other studies.

Key words: Drug intake, Poisoning, Outcome

Özet

Giriş: İlaç intoksikasyonları acil servise başvuruların önemli bir kısmını oluşturmaktadır, yoğun bakım yatışlarının da önemli bir kısmından sorumludur. Özellikle çoklu ilaç alımları öngörülmesi zor mortalite ve morbidite nedeni olabilmektedir.

Materyal-Metod: Çalışmamızda, acil servisimize ilaç alımı sonrası zehirlenme ile başvuran hastaların başvurularındaki kan parametreleri, yatış durumları ve özgeçmişlerine ait bazı özellikler retrospektif olarak değerlendirildi. Hastaların acil servis başvurusunda alınan pH, laktat, beyaz küre, hemoglobin, trombosit, alaninaminotransferaz, aspartataminotransferaz değerleri ile hastanın servis yatışı, yoğun bakım yatışı, taburculuk kararı ve mortalite arasındaki ilişki incelendi. Hastaların yatış durumu ile ilgili veriler de ortaya konuldu.

Bulgular: Toplam 80 hasta çalışmaya dâhil edildi. Hastaların 47'sinin servis yatışı(%58.75), 23'ünün yoğun bakım yatışı(%28.75), 4'ünün acil servisten taburcu olduğu(%5), 6'sının ise tedavi red veya izinsiz terk(%7.5) ile hastaneden ayrıldığı saptandı. Acil servis başvuru anında bakılan kan parametreleri ile hastaneye yatış durumu arasında anlamlı ilişki saptanmadı.

Tartışma: Çalışmamızda acil servisten yoğun bakıma yatan hasta sayısı diğer çalışmalara göre yüksek saptandı.

Anahtar Sözcükler: İlaç, Sonlanım, Zehirlenme

Giriş

"Zehir" kelimesi ilk defa M.Ö.1230 senesinde ölümcül maddelerden hazırlanan ilaç ve iksir olarak tanımlanmasına rağmen, zehir ve zehirlenmenin tarihçesi binlerce yıl öncesine dayanmaktadır. Toksik olabilecek miktarda bir ajana maruz kalma sonucu oluşan klinik duruma 'zehirlenme' denilmektedir. Zehirlenmeler tüm dünyada önemli mortalite ve morbidite nedenidir. Zehirlenmeler; kaza ile(sıklıkla çocuklarda), intihar amaçlı, çevresel ya da mesleki maruziyet, terapötik hata(yanlış ilaç, doz ve hasta, ilaç-ilaç etkileşimi gibi), ilaçlara bağlı yan etkiler, ilacın kötüye kullanımı, besin zehirlenmeleri, hayvan ısırmaları, kimyasal ve biyolojik ajanlar ile savaş gibi nedenlerle olabilmektedir. Kaza sonucu veya kasıtlı zehirlenmeler ile uyuşturucu madde kullanımı dünya genelinde morbidite, mortalite ve sağlık harcamalarının önemli bir kaynağını oluşturmaktadır. Az gelişmiş ülkelerde tarımsal pestisitlere bağlı zehirlenmeler daha sık görülmekte iken, gelişmiş ülkelerde en çok intihar amacıyla ilaç alımına bağlı zehirlenmeler ile karşılaşılmaktadır. Ülkemizde en sık zehirlenme nedenleri; ilaçlar, karbonmonoksit, gıda, mantar, organofosfat ve koroziv maddelerdir. Zehirlenme olguları acil servislere başvuruların %0.8-5 kadarını oluşturmakta ve bu vakaların bir kısmı yoğun bakıma yatırılarak tedavi edilmektedir[1]. Zehirlenmeler 14 yaş ve altındaki olguların %63'ünde 1-4 yaş arasında iken, 14 yaş üstünde en sık 25-35 yaş grubunda görülür ve kadın/erkek görülme oranı 63/37'dir[2,3]. Zehirlenmelere bağlı ölüm oranı gelişmiş

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ülkelerde %1 iken, gelişmekte olan ülkelerde bu oran %3-5 arasındadır[3].

Biz bu çalışmamızda, ilaç zehirlenmesi ile acil servise başvuran hastaların mortalite, morbiditeleri ve yoğun bakım yatış karalarının başvuruları sırasında alınan kan tetkikleri ile öngörülebilirliğini araştırmayı ve bu hastaların verilerini sunmayı amaçladık.

Materyal ve Metod

01.01.2018 ile 01.07.2018 tarihleri arasında hastanemiz acil servisine zehirlenme nedeniyle başvuran hastalar çalışmamıza dâhil edildi. 90 hastanın dosyası sistem üzerinde geriye dönük olarak incelendi. 18 yaş altında olanlar ile fare zehiri, bonzai, organofosfat, kostik madde ve böcek kovucu alanlar çalışma dışı bırakıldı. Toplam 80 hasta çalışmaya dâhil edildi. Hastaların yaşı, cinsiyeti, zehirlenmeye neden olan ilaç veya ilaçların isimleri, hastanın aldığı miktar, laboratuar değerleri (laktat, pH, beyaz küre, hemoglobin, trombosit, alaninaminotransferaz, aspartataminotransferaz) ile taburculuk, servis yatışı veya yoğun bakım yatışı durumları incelendi.

Elde edilen veriler Statistical Package For The Social Sciencesfor Windows 23 (SPSS, Chicago, IL, USA) programı ile analiz edildi. Kantitatif veriler ortalama±standart sapma, kalitatif veriler ise sıklık ve yüzde olarak sunuldu. Gruplar arasındaki ilişki için Chi-Square testi kullanıldı. P<0.05 istatistiksel olarak kabul edildi.

Bulgular

Toplam 80 hasta çalışmaya dâhil edildi. Hastaların 56'sı kadın (%70), 24'ü erkek(%30) idi. Hastaların yaş ortalaması 29,7±13,4 yıl (2-67) idi. Tek ilaç kullanımı ile 20 hasta (%25) başvururken 60 hasta (%75) ise çoklu ilaç alımı sonrası başvurmuştur. Hastaların büyük bir çoğunluğunda tedavi için hastaneye yatış gerekmiştir. Hastaların 47'si (%58.75) servise yatarken, 23'ü (28.75) yoğun bakıma yatmıştır. Hastaların 4'ünün (%5) acil servisten taburcu edildiği, 6'sının (%7.5) ise tedavi red veya izinsiz terk ile hastaneden ayrıldığı saptandı. Çalışmanın yapıldığı tarihlerde bu zehirlenme olgularından sadece 1 hasta hayatını kaybetmiştir. Kan parametrelerine ait veriler Tablo 1'de gösterilmiştir. Hastaların acil servise başvuruları sırasında bakılan kan parametrelerinin hastaların yoğun bakım, servis yatışı veya taburculuk kararı verilmesinde etkili olup olmayacağı incelenmiş, aralarında korelasyon olup olmadığı araştırılmıştır ve bu parametrelerle ilgili hastaların yatış kararını etkileyecek anlamlı bulgu saptanmamıştır. Hastaların tek bir ilaç alması ile çoklu ilaç alımlarının akıbet durumu ile karşılaştırılması Tablo 2'de verilmiş olup aralarında istatistiksel olarak anlamlı bir ilişki bulunamamıştır (p>0,05).

Tartışma

Tüm dünyada acil servislere zehirlenme nedeni ile çok sayıda hasta başvurmaktadır ve hastaların klinik durumları-

Tablo 1. Kan parametrelerine ait veriler

	Ortalama±SS	Minimum	Maksimum
Ph	7,39+0,05	7,30	7,61
Laktat	2,32+2,12	0,80	16,00
Beyaz Küre	17,52+66,76	4,11	601,00
Hemoglobin	12,79+1,84	7,20	16,60
Trombosit	253,61+63,24	72,00	435,00
ALT	18,01+8,17	9,00	45,00
AST	21,88+9,31	11,00	60,00

***SS:** Standart sapma; **AST:** Aspartat Amino Transferaz; **ALT:** Alanin Amino Transferaz*

Tablo 2. Hastaların aldığı ilaç miktarına göre acil servis sonlanımının karşılaştırılması

Taburcu		Acil Servis Sonlanımı			p
		Yatış	Tedavi Red		
Alınan İlaç Miktarı	Tek İlaç	4	52	4	0,455
	Çoklu İlaç	0	18	2	

na göre yoğun bakım yatışı, servis yatışı veya taburculuk planlanmaktadır. Yapılan çalışmalarda zehirlenmelere bağlı yoğun bakım yatış oranının %3 ile 6 arasında olduğu belirtilmektedir [4,5]. Bizim çalışmamızda ise bu oran %32.5 bulunmuştur. Literatürde paylaşılan çalışmalarda yoğun bakıma yatış kararı verilirken hastaların klinik durumlarına göre karar verildiği görülmektedir. Çalışmamızda bu oranın yüksek saptanmasına, 114 Ulusal Zehir Danışma Merkezi'nin önerisi ile hastalara yoğun bakım yatışı planlanmasının neden olabileceğini düşünmekteyiz. Muzaffer Özenir ve ark. yaptığı çalışmada altmış yedi olguda tek ilaç (%66.3) ve 34 olguda çoklu ilaç (%33.7) zehirlenmesi bildirmişlerdir. Bizim çalışmamızda ise hastaların %25'inde tek ilaç kullanımı söz konusu iken, %75'inde ise çoklu ilaç alımı mevcuttur. Muzaffer özenir ve ark. yaptığı çalışmada tek ilaç alımının yüksek olmasının sebebinin çocuk hastaların fazlalığı nedeniyle kazara alımlardan kaynaklandığı sonucuna varılmaktadır. Bizim çalışmamızda hastaların tümünün erişkin olması dolayısı ile kazara alım az sayıda saptanmıştır. Yapılan başka çalışmalarda çoklu ilaç kullanım oranı %64.9, %53.5 olarak verilmiştir[6,7]. Erişkin hastalar ile yapılan bu çalışmalarda bizim çalışmamıza benzer şekilde çoklu ilaç alımı oranı daha yüksektir.

Laktat doku hipoksisi düzeyini belirlemek için kullanılan önemli bir belirteçtir. Kandaki laktat seviyesinin ölçümü ise günümüz teknolojisi ile kolay hızlı ve ucuz olarak sağlanmaktadır. Kan laktat düzeyi normal aralığı 0,5-1,8 mmol/L'dir. Yapılan çalışmalarda kan laktat düzeyi 2mmol/L altında olan hastaların mortalite ve morbiditesi düşükken, kan laktat düzeyleri 10mmol/L'ye yaklaşan hastaların çoğunda mortalite ve morbidite oranında artış görülmektedir[9,10]. Ayrıca metformin gibi bazı ilaçlar da laktat yüksekliğine sebep olabilmektedir. Biz de çalışmamızda laktat değeri ile hastaların yoğun bakım, servis veya taburculuk durumu arasındaki ilişkiyi karşılaştırdık. Laktat değeri yüksekliği ile yoğun bakım yatış kararı arasında anlamlı korelasyon saptanmadı. Çalışmaya dâhil edilen hastalarda değerlendirilen kan gazı örnekleri acil servis başvurusu sırasında alınan kan gazı olduğundan ve bu hastalarda hastaneye başvuru süresi kısa olduğu için anlamlı sonuç saptanmamış olabileceğini düşünmekteyiz. Hastanın gelişinde alınan kan gazı, alınan ilaçların henüz hastanın metabolik durumuna etki etmeyeceği için yoğun bakım, servis veya taburculuk kararı verilmesinde etkili olmadığını düşündürmektedir. Laktat ve pH değerleri hastanın yoğun bakım, servis yatış veya taburculuk kararlarını değiştirmese bile hastanın acil servisteyken tedavisinin düzenlenmesinde önemli bir yere sahiptir. Hastanın takibinde laktat değerinde artış görülmesi zehirlenmeye sebep olan ilacın sistemik etkilerinin başlaması sonucu gerçekleşebilir ve bu durum yoğun bakım kararını etkileyebilir, bu konu ile ilgili çalışma yapılması gerekmektedir.

Çalışmamızda hastaların acil servis başvurularında alınan beyaz küre, hemoglobin, trombosit, alaninaminotransferaz ve aspartataminotransferaz değerleri ile hastanın yoğun bakım yatışı, servis yatışı ve taburculuk kararı arasındaki ilişki araştırıldı ve anlamlı bir ilişki saptanmadı. Bunun sebebinin hastaların zehirlenmeye neden olan ilaç alımından acil servise başvurana kadar geçen sürenin kısa olması ve bu durumunda alınan ilaçların henüz metabolik bir değişikliğe neden olmaması olduğu düşünülmektedir.

Hastaların acil serviste devam eden gözlemlerinde alınan ardışık kan parametreleri hastaların yoğun bakım ihtiyaçlarını belirlemede etkili olabilir. Bu konu ile ilgili daha çok çalışmaya ihtiyaç vardır.

Çalışmamızın sınırlılıkları; geriye dönük bir çalışma olması, vaka sayısının az olması, çalışma süresinin kısa olmasıdır.

Sonuç

Çalışmamızda acil servisten yoğun bakıma yatan hasta sayısı diğer çalışmalara göre yüksek saptanmıştır. Bunun nedeni olarak her hasta için 114 ulusal zehir danışma merkezinin aranması ve telefon üzerinden hastanın aldığı ilaçlara göre yoğun bakım ihtiyacının belirlenmesi olabileceği düşünülmektedir. Hastanın klinik durumuna göre hastayı değerlendiren hekimler tarafından yoğun bakım ihtiyacı belirlenirse yoğun bakım yatışları azalabilir. Bu konu ile ilgili çalışmalara ihtiyaç vardır.

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Case Report

Eurasian Journal of Toxicology

Sıvı Gübre İnhalasyonu: Olgu Sunumu

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Abstract

Turkey is an agricultural country. Liquid fertilizer is widely used by agricultural workers. Poisoning with liquid fertilizer is mainly due to inhalation of poison by the airways, but cases of oral poisoning are also reported. Although inhalation of liquid fertilizers is a rarely seen clinically, it can cause serious mortality and morbidity. In this case report, we aimed to present a 27- year -old male patient who was exposed to liquid fertilizer by inhalation by taking the consent of the institution and the patient consent form.

Key words: Inhalation, Intoxication, Liquid fertilizer

Özet

Türkiye bir tarım ülkesidir. Sıvı gübre zirai işlerde çalışanlar tarafından yaygın biçimde kullanılmaktadır. Sıvı gübre ile zehirlenme, daha çok solunum yolları aracılığı ile zehrin solunmasına bağlı olarak görülmekle birlikte, oral yoldan zehirlenme vakaları da bildirilmektedir. Sıvı gübre inhalasyonu, klinik olarak nadiren gözlense de ciddi morbiditeye ve mortaliteye neden olabilir. Biz bu olgu sunumumızda; inhalasyon yoluyla sıvı gübreye maruz kalan, 27 yaşında erkek hastayı kurum izinleri ve hastadan onam formunu alarak sunmayı amaçladık.

Anahtar Sözcükler: İnhalasyon, İntoksikasyon, Sıvı gübre

Giriş

Dünya nüfusu gittikçe artmakta ve açlık önemli bir sorun olarak görülmektedir. Üretimi attırmak amacıyla yaygın biçimde tarım ilaçları ve gübre kullanılmaktadır. Uygulanan tarım ilaçları ve gübrelerin bir kısmı böcek tarafından alınmakta geriye kalan kısmı ise yer altı ve yüzey suyuna karışarak bitki, hayvan ve insan sağlığını tehdit edebilmektedir. Kanser dahil pek çok hastalıkların etiyolojisinde gübrelerden içme sularına karışan nitratlar sorumlu tutulmaktadır[1]. Bu ilaçları kullanmadan önce toprak analizlerinin iyi yapılıp uygun dozda ve bilinçli uygulamalarla yapılması gereklidir. Sıvı gübre ülkemizde meyve ve sebze yetiştiriciliğinde sıkça kullanılmaktadır[3]. Sıvı gübre kullanımına bağlı olarak gelişen zehirlenme olgularına literatürde oldukça nadir rastlanmaktadır. Biz bu olgu sunumunda, sıvı gübre inhalasyonuna bağlı olarak intoksikasyon gelişen hastamızı sunuyoruz.

Olgu Sunumu

27 yaşında erkek hasta takipne ve yüzünde kasılma şikayeti ile acil servise başvurdu. Öyküsünde, içinde sıvı gübre bulunan şişeyi açtıktan sonra baş dönmesi ve bulantı şikayeti olduğu ve inhalasyondan 1 saat sonra acil servise başvurduğu öğrenildi. Yapılan fizik muayenesinde, nabız 90 dk, kan basıncı 110/70 mmHg, oksijen satürasyonu %92 olarak ölçüldü. Hastanın nörolojik muayenesinde bilinci açık, kooperasyon ve oryantasyonu tam, pupiller izokorik ışık refleksi pozitif olarak tespit edildi. Glaskow koma skalası 15 puan olarak değerlendirildi. Hastaya serebrovasküler olay (SVO) ön tanısını ekarte etmek için bilgisayarlı tomografi (BT) planlandı. kan gazı analizlerinde pH:7.46, pO2:44.4 mmHg, pCO2: 31.1 mmHg, HCO3:22.6 mEq/dL ve Methemoglobin (MetHb):1.2, C-reaktif protein (CRP) ve beyaz küre değerleri yüksek olarak bulundu. Çekilen beyin BT normal olarak raporlanan hasta, sıvı gübre inhalasyonuna bağlı zehirlenme tanısı ile yoğun bakıma yatırıldı. Hastaya (500 mg/5 ml) As-

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korbik asit, (300 mg/3 ml) Asetilsistein, dispeptik yakınmaları için (50 mg/2 ml) dozunda Ranitidin, olası aspirasyon pnömonisi riski nedeniyle intra venöz (İV) yoldan 1 gram Seftriakson verildi. Hasta, 4 gün yoğun bakım takibi sonrasında servise nakil edildi. Servis takiplerinde herhangi bir şikayeti olmayan hasta 1 gün servis takibi sonrasında taburcu edildi.

Tartışma

Bir ülkenin gübre üretimi ve tüketimi tarımsal gelişmesinde önemli bir belirteç olarak kabul edilmektedir. Bitkiler için mutlak gerekli elementlerden biri azottur. Azot (N) bitkilerin en fazla ihtiyaç duyduğu ve toprakta yıldan yıla yenilenmesi gereken bir bitki besin elementidir. Günümüzde kullanılan suni gübreler içerisinde en yüksek payı azotlu gübreler almaktadır. Azotlu gübrelerin ardından tüketim bakımından ikinci sırada potasyumlu gübreler (K2O) bulunmaktadır[4,5]. Olgumuzda intoksikasyona neden olan sıvı gübre içerik olarak (N ve K2O) içermekteydi. Azot basit asfiksi oluşturan gazlar arasında yer almaktadır. Azot inhalasyonuna bağlı gelişen asfiksi varlığında yapılması gereken ilk müdahale hastanın temiz havaya çıkarılması, temiz suyla yıkanmasıdır. Uzun süreli maruziyette kalp ve santral sinir sistemi gibi hipoksiye daha duyarlı organlarda sekel gelişebilir[6]. Bu gaz methemoglobinemi de oluşturduğu için, bu yolla oksijen taşıma kapasitesi ve dokuların oksijen alımının azalması sonucu sistemik toksisite belirtileri de ortaya çıkabilir[7,8].

Azot zehirlenmelerinde erken tanı ve tedavi zehirlenme olgularına yaklaşımda için en önemli parametredir. Sıvı gübreye bağlı zehirlenmeler kaza sonucu maruziyet veya özkıyım amaçlı alımlar olmaktadır. Sıvı gübre kullanımında firma tarafından belirlenmiş bir kullanım talimatı mevcuttur. Hastamız sıvı gübreyi kısa süreli inhale ederek kaza sonucu maruziyet şeklinde zehirlenmiştir. Askorbik asit, methemoglobinemi durumunda methemoglobinemi düzeyini azaltan ajanlardandır[9,10]. Asetilsistein balgam hacmini ve yoğunluğunu azalttığı ve atılımını kolaylaştırdığı öksürük ve nefes darlığını azalttığı saptanmıştır[11]. Biz de hastamızda olası methemoglobinemi gelişebileceğini düşündüğümüz için askorbik asit ve olası akciğer hasarı ihtimaline karşın asetilsistein tedavisi verdik. Literatürde azot ve K2O içerikli sıvı gübre intoksikasyonuna dair çalışmaya yada olgu sunumuna rastlamadık. Klinik verilerimizi bu yüzden kıyaslama şansımız bulunmamaktadır. Kim ve ark. sıvı kalsiyum gübre kullanımına bağlı gelişen intoksikasyon hastasında dispne, hareketsizlik ve hiperakut hiperkalsemi bulguları gelişmiştir[12]. Bayram ve ark. amonyak inhalasyonuna bağlı gelişen intoksikasyon hastalarında gelişen pulmoner komplikasyonlarsonrasın tedavisinde noninvazif mekanik ventilasyon uygulamışlar[13]. Olgumuzda noninvazif mekanizk ventilasyon uygulamasını gerektirecek ciddi patolojiler gelişmedi.

Sonuç

Ülkemiz tarım ülkesidir ve tarımın yoğun olarak yapıldığı jeopolitik coğrafyada yer almaktadır. Bu alanda çalışan insanlar başta gübre olmak üzere tarımda kullanımı olan birçok kimyasala maruz kalmaktadır. Vakamızda olduğu gibi tarım ilaçlarına bağlı kazara zehirlenmeler görülebilir. Başta gübre olmak üzere diğer kimyasalların kullanımlarına yönelik olarak hem üreticilerin hem de tüketicilerin eğitilmeleri gereklidir. Ayrıca satılan kimyasal ürünlerin üzerine dikkat çekici olarak büyük puntolarla yazılacak kullanım talimatları olası zehirlenmelerin önüne geçmede katkıda bulunabilir. Bu ürünlerin kullanımı esnasında gözlük, eldiven, maske gibi koruyucu ekipman kullanımı önerileri de eklenebilir.

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Case Report

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Neutropenic Toxic Epidermal Necrolysis Due to Sulphonamide Use

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Abstract

Toxic epidermal Necrolysis (TEN), which has high mortality and morbidity rates, often develops after medication. Clinically, at least 30% of the mucous membranes and skin are involved. Neutropenia is very rare in TEN cases and is directly related to mortality. We wanted to share a case diagnosed with TEN who developed neutropenia during follow-up and was discharged with full recovery with early diagnosis and effective treatment.

Key words: Cotrimoxazole, Toxic epidermal necrolysis, Neutropenia

Özet

Yüksek mortalite ve morbidite oranlarına sahip toksik epidermal nekroliz (TEN) genellikle ilaç tedavisinden sonra gelişir. Klinik olarak, mukoza ve cildin en az% 30'u tutulur. Nötropeni TEN olgularında çok nadir görülür ve doğrudan mortalite ile ilişkilidir. Takip sırasında nötropeni gelişen ve erken tanı ve etkili tedavi ile tam iyileşme ile taburcu edilen TEN tanılı bir vakayı paylaşmak istedik.

Anahtar Sözcükler: Nötropeni, Kotrimaksazol, Toksik epidermal nekroliz

Introduction

Trimethoprim-sulfamethoxazole (TMP / SMX) is an antibiotic that acts by inhibiting the enzymes involved in the synthesis of tetrahydrofolic acid in bacteria. Although both molecules are bacteriostatic, when used together they block the enzymes and show bactericidal action[1]. Toxic epidermal necrolysis (TEN) is a condition with high mortality and morbidity, often associated with skin and mucosal involvement, against drugs. It is most commonly seen after drug use and sulfonamides are included in this group. Neutropenia is a considerably rare laboratory finding in patients with TEN and is directly related to mortality[2].

Case

A 36-year-old female patient was admitted to the emergency department with complaints of fever, weakness, general malaise, rashes on the torso, arms and legs and a painful lesion in the mouth. Physical examination revealed maculopapular lesions and sporadic vesiculobullous lesions in the upper extremity, frictional bullous lesions (30-40%) **(Figure A-B)** with maculopapular lesions in the dorsum, several bullous and erode lesions in the oral mucosa, and redness in both eyes, mostly in the right eye. In her history, sulfonamide (trimethoprim / sulfamethoxazole) was administered prophylactically 3 days before, after c-section. The patient was hospitalized with a pre-diagnosis of TEN. TMP/SMX treatment was discontinued. Methylprednisolone treatment at a dose of 1 mg/kg and a fluid-electrolyte replacement was started. Urine, blood, and skin cultures were taken. HIV tests were requested. No pathology was detected in routine laboratory tests. In the first week of the treatment, widespread maculopapular and sporadic vesiculobullous lesions, increase of erode bullous lesions especially on the right upper extremity and dorsum, targetoid and sporadic bullous lesions on the lower extremities (80%) **(Figure C-D)**, advancement in the oral lesions and a regression in the neutrophil count to 1000 10^3/ mm^3 were observed. Bullous lesions of the patient were carefully drained, only necrotic lesions were debrided, and the dressing was performed with silver sulfadiazine-free antiseptic agents daily. On the 20th day of treatment, lesions

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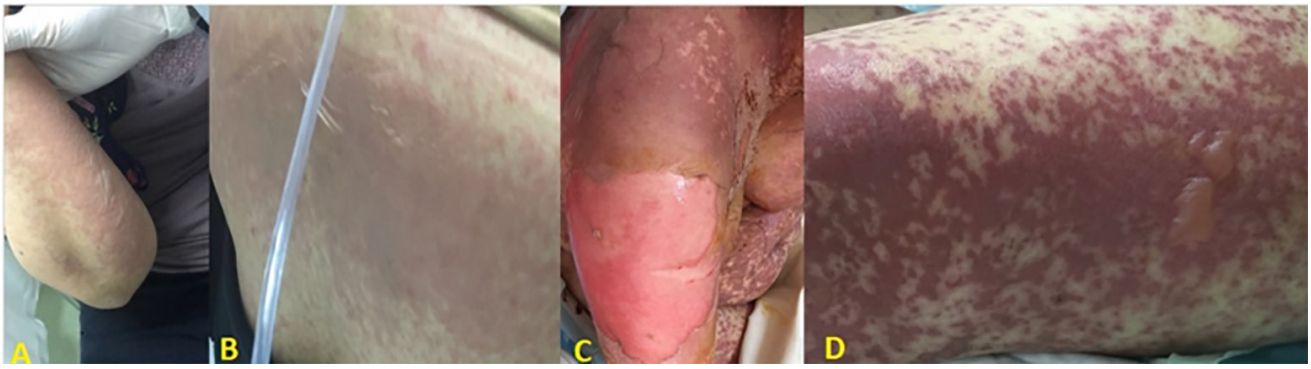

regressed and the neutrophil count increased. After 30 days of corticosteroid and supportive therapy, the lesions healed completely, leaving postinflammatory hyperpigmentation, nail onychomadesis and alopecia in the hair.

Discussion

Toxic epidermal necrolysis (TEN) is a condition with high mortality and morbidity, often associated with skin and mucosal involvement, against drugs. It is clinically characterized by epidermal dissociation in at least 30% of the body involving at least 2 mucosal areas, diffuse purpura, and non-typical target-like lesions[3].

Patients with viral diseases (HIV, hepatitis, herpes, etc.), immunosuppressed patients, patients with a previous diagnosis of TEN of themselves or their families are at risk for this condition[4]. After recent studies, the high rates of HLA-A29, HLA-B12, and HLA-DR7 positivity in TEN cases have shown that it is possible to create risk groups in terms of genetic susceptibility.

The most important risk factor for TEN is drugs with 80-95%. Although the risk of TEN has been reported for more than 200 drugs, the most common drugs with TEN risk are allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, sertraline, and sulfonamide group antibiotics (especially trimethoprim/sulfamethoxazole). 5% of the cases are idiopathic[5]. The disease shows up most commonly between 1. and 3. weeks after the drug intake, but it can be observed to come up until 60 days[6].

The pathogenesis of the disease is unknown, but it is thought to be a cytotoxic immune reaction to an antigen on the surface of keratinocytes[7].

At least 50% of patients have prodromal symptoms (fever, weakness, headache, rhinitis, sore throat, itching of the eyes, myalgia, etc.) that may be mistaken for the signs of upper respiratory tract infection. In addition to these complaints, mucosal lesions are symptoms of the disease. Erythema in the mucous membranes gradually develops into painful hemorrhagic bullae. Crusts show up as grayish pseudomembrane on the lips and then appear as hemorrhagic[8]. Photophobia, pain, lacrimation, chemosis, and redness may occur due to eye involvement. Corneal ulceration, anterior uveitis, and purulent conjunctivitis may develop in patients with more severe involvement. Finally, these lesions may cause blindness[9]. Genital mucosal involvement appears as painful erosion on the glans penis, vulva, and vagina, burning during urination and urinary retention. Acute tubular necrosis, hematuria, and microalbuminuria may occur in the acute phase[10]. Anemia, mild elevation of hepatic enzymes and amylase elevation may be observed and not have a significant effect on prognosis. Neutropenia is a very rare laboratory finding and is directly related to mortality. It is so rare that it was not included in '*Severity of Illness Score for TEN'* (SCORTEN), which is a prognostic marker for TEN[2]. Although neutropenia, which is very rare and mortal, developed in our case, it was cured fully after treatment.

A multidisciplinary approach is important in the treatment of TEN. Drugs used until 2 months ago should be questioned and all suspicious drugs should be discontinued. Patients should be admitted to intensive care or burn units. The room temperature should be kept between 28-32 ° C, especially in those with large surface area involvement. Intubation may be considered in patients with severe airway involvement, airway obstruction, acute respiratory distress syndrome, and in patients in the need for sedation due to excessive pain. TEN patients should be considered as burn patients and adequate fluid replacement should be given. Pain treatment is the most important treatment for these patients and morphine derivatives are recommended. Prophylactic antibiotics are not recommended, but if proliferation occurs in skin, blood and urine cultures, the causative agent should be initiated[11].

The use of intravenous immunoglobulin did not improve survival in patients with TEN. Cyclosporine was found to reduce mortality in adults and progression of epidermal decomposition (dose: 3 mg / kg / day for 10 days and reduced and ended by 30 days)[12]. Systemic corticosteroids have been clinically effective in healing and are currently the most commonly used agent for drug side effects. In recent studies, anti-TNF agents are looking promising in TEN diseases[13].

Conclusion

The companion of neutropenia in the presence of TEN, which has very high rates of mortality and morbidity, makes the prognosis worse. With our case, we wanted to share that even this patient group could be discharged with full recovery with early diagnosis and effective treatment.

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