

ZEHİRLENMELERDE ANTİDOT TEDAVİSİ

Doç Dr Özlem GÜNEYSEL

Dr LÜTFİ KIRDAR KARTAL EAH

ACİL TIP KLİNİĞİ

Proposed list of specific antidotes in the European Community (Council of Europe, 1990)

Antidote	Indication/toxic agent
Acetylcysteine	Paracetamol; carbon tetrachloride
Amyl nitrite	Cyanide
Antivenins and antitoxins	
Atropine	Cholinergic syndrome
Benzylpenicillin	Amanitotoxins
Calcium gluconate	Hydrogen fluoride; fluorides; oxalates
Calcium disodium edetate	Lead
Dantrolene	Malignant hyperthermia; malignant neuroleptic syndrome
Deferoxamine	Iron; aluminium
Diazepam	Seizures; chloroquine
Dicobalt edetate	Cyanide
Digoxin-specific (Fab) antibody fragments	Digoxin; digitoxin; digitalis glycosides
Dimercaprol (BAL)	Arsenic; gold; inorganic mercury
4-Dimethylaminophenol	Cyanide
Diphenhydramine	Drug-induced dystonias
Ethanol	Methanol; ethylene glycol
Etybenzatropine (ethybenztropine)	Drug-induced dystonias
Flumazenil	Benzodiazepines
Folinic acid	Folic acid antagonists
Glucagon	Beta-blockers
Hydroxocobalamin	Cyanide
Methionine	Paracetamol
4-Methylpyrazole	Methanol; ethylene glycol
Methylthioninium chloride (methylene blue)	Methaemoglobinaemia
N-Acetylpenicillamine	Mercury (organic and elemental)
Naloxone	Opiates
Neostigmine	Neuromuscular block (curare type); peripheral anticholinergic poisoning
Oximes	Organophosphates
Oxygen	Carbon monoxide; cyanide; hydrogen sulfide
D-Penicillamine	Copper; gold; lead; mercury (elemental); zinc
Pentetic acid (DTPA); diethylene-triamine pentaacetic acid	Plutonium; actinides
Phentolamine	Alpha-adrenergic poisoning
Physostigmine	Central anticholinergic syndrome from atropine and derivatives
Phytomenadione	Coumarin and indanedione anticoagulants
Potassium ferric hexacyanoferrate (Prussian blue)	Thallium
Prenalterol	Beta-blockers
Protamine sulfate	Heparin
Pyridoxine (Vitamin B6)	Isoniazid; crimidine; gyromitrin; hydrazines
Silibinin	Amanitotoxins
Sodium nitrite	Cyanide
Sodium thiosulfate	Cyanide
Succimer (DMSA) Dimercaptosuccinic acid	Lead; mercury (inorganic and organic); arsenic
Tolonium chloride (toluidine blue)	Methaemoglobinaemia
Trientine (triethylene tetramine)	Copper
Unithiol (DMPS) 2,3-dimercapto-1-propanesulfonic acid	Mercury (methyl- and inorganic); lead



Yazılı tarih öncesinden bu yana
n eklemek için simgeyi
evrensel antidot aranıyor
in

Nicander of Colophon
(Ahmetbeyli, Izmir)



Nikander, "*Theriaca*", 10th century,
Constantinople

Yunanlılar evrensel antidotu aleksifarmika veya tearik olarak adlandırdılar. Aleksifarmika terimi zehirden sakınmak anlamındaki aleksifarmakos ve antifarmakon veya antidot kelimelerinden oluşmaktadır. Aleksifarmika zaman içinde giderek, kuştüyü kullanarak kusmayı indükleme gibi tedavi yöntemleri için kullanılmaya başlandı [3]. Milattan önce 5. yüzyıldan itibaren adsorban bir ajan olan terra sigillata veya kutsal mühürlü toprak evrensel antidot olarak kabul edildi. Bu ajan sadece Yunan Adalarından Lemnos'ta bulunan kırmızı bir çamurdan oluşuyordu ve tüm zehirlerin üstesinden gelinmesinde etkin olduğu düşünülüyordu. Tarih boyunca evrensel antidotlar olarak taraftar toplayan birçok diğer ajan varolmuştur: bezoar taşları (intestinal taşlar), fosil taşları ve efsanevi tek boynuzlar.

Antidot...

5

- Hayal kurmak güzeldir...
- Klinik zorunluluklarından ayrı olarak toplumsal ve duygusal beklenti

Tarihçe

6

- Tarihte zehirlenmeler kazara / bilinçli (?)
- Zehirlenmelere karşı kullanılan ilk yöntem ***“kusturma”***
- 1800'lere kadar genellikle bitkisel kaynaklı (daha az hayvansal ve mineral katkı)
- Ortodoks doktorların humoral tedaviyi keşfinden sonra cesitlendi (hayvan kanı, zehirleri, boynuzu, vb)

Tarihçe

7

- “Unicorn’s corn”
- “Bone of a stag’s heart”
- “Limni toprağı”





Sonraları ..

- “*Panzehir*” (antidot)
L. antidotum, Gr. antidoton ve modern tıp
- “*Bir zehiri etkisiz hale getirmek (kimyasal antidot) ya da fizyolojik etkileriyle savaşmak (fizyolojik antidot) için tedavide kullanılan madde.*”

Antidot



- Yetim ilaç (*Orphan drug*) statüsündedirler
- Üretim maliyetleri yüksek,
- İmalat ve ruhsatlandırılması belirli ülkelerde gerçekleştirilen,
- Normal bir ilaç olarak üretilmesi ve ruhsatlandırılması zorunluluğu olmayan,

Antidot

Antidotlar hakkında bilgiler,
uluslararası organizasyonlar
tarafından yayınlanır:

- IPCS INTOX Databank
- IPCS INCHEM
- IPCS Poisons Information Monographs
- IPCS Treatment Guides
- IPCS/European Commission Evaluation of Antidote Series (IPCS INCHEM, 2006)
 - Antidotes for poisoning by cyanide
 - Antidotes for poisoning by paracetamol
 - Naloxone, flumazenil and dantrolene as antidotes
 - Deferoxamine
 - Fralidoxime (in preparation)
 - Obidoxime (in preparation)
- IPCS Guidelines for the Prevention of Toxic Exposures
- IPCS International Chemical Safety Cards (ICSCs)
- IPCS Environmental Health Criteria Monographs (EHCs)
- CCOHS CHEMINFO Database
- WHO/FAO Information Documents
- UK Poison Information Documents (UK PIDs)
- International Agency for Research on Cancer monographs (IARC)



Available online at www.sciencedirect.com



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TOXICOLOGY

www.elsevier.com/locate/toxicol

The dilemma of approving antidotes

Christian Steffen*

Clinical Trials Unit, Federal Institute for Drugs and Medical Devices, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany

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Available online 1 December 2006

Antidot Referans Bilgi Kaynakları

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The International Programme
on Chemical Safety (IPCS)



- WHO (World Health Organisation)
- UNEP (United Nations Environment Programme)
- ILO (International Labour Organisation)

Antidot Referans Bilgi Kaynakları

13

<http://www.who.int/ipcs/poisons/centre/en/index.html>

The International Programme on Chemical Safety (IPCS)



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Poisons centres

What is a poisons centre?

A poisons centre is a specialized unit that advises on, or assists with, the prevention, diagnosis and management of poisoning. The structure and function of poisons centres varies around the world. At a minimum a poisons centre is an information service. Some poisons centres may also include a toxicology laboratory and/or a clinical treatment unit.

What does a poisons centre do?

A poisons centre provides an emergency poisons information service. It may also provide an analytical toxicology service and a clinical service. In addition the poisons centre may play an important role in developing contingency plans for, and responding to, chemical disasters, and may be involved in monitoring the adverse effects of drugs, and in handling problems of substance abuse. It may also be involved in research, education and training.

Poisons Information Service

The poisons information service is concerned with the risk assessment, diagnosis, management and prevention of exposure to any substance, by any route, in patients of any age, and arising from any circumstance, be it accidental, intentional, occupational etc. In addition the poisons centre can provide general information about substances, their properties and toxicity.

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[World directory of poisons centres](#)

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Essential tools for chemical safety
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ON CHEMICAL SAFETY**



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awareness activities**



**Published by the World Health Organization in collaboration with
the United Nations Environment Programme and
the International Labour Organization**

Antidot Referans Bilgi Kaynakları

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- AB Komisyonu, 1990;
- EMEA (The European Medicines Agency)





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SCIENCE MEDICINES HEALTH

An Agency of the European

Text size: A A A

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09/09/2010

European Medicines Agency holds international workshop on clinical trials in the context of global medicines development

Participants from around the world emphasise the need for cooperation to ensure a robust global framework for clinical trials ... [Read more](#)

08/09/2010

CHMP meets to discuss Avandia and Pandemrix

The Committee for Medicinal Products for Human Use (CHMP) met on Wednesday 8 September to discuss the ongoing benefit-risk review of the rosiglitazone-containing

[2015 Roadmap](#)

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Antidot üretimi

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- Sürekli kullanıma gereksinim olmaması ve buna bağlı raf ömürlerinin tükenmesi nedeniyle finansman desteği gereklidir.
- Yeni antidot üretimi için finansal destek olmadığından; durumları yetim ilaç (*Orphan drug*) pozisyonundadır ve aynı yasal avantajlara sahiptirler.



Med Clin N Am 89 (2005) 1379–1397

THE MEDICAL
CLINICS
OF NORTH AMERICA

New Developments in Antidotes

Nicole L. Ries, PharmD^{a,*},
Richard C. Dart, MD, PhD^{a,b}

^aRocky Mountain Poison and Drug Center, Denver Health, Denver, CO, USA

^bUniversity of Colorado Health Sciences Center, Denver, CO, USA

Orphan Medicinal Products (OMP)

20

- Nadir görülen ciddi, hayatı tehdit edici veya kronik yetisizliğe neden olabilecek hastalıklara karşı üretilirler (Genel yaklaşım ~5/10.000 kişi).
- İlk tanımlama..
 - US Orphan Drug 1983
 - Japonya 1993
 - Avustralya 1998

- Akut zehirlenmelerde antidot uygulaması için aydınlatılmış onam alınmaz ! (?)
- Yasal düzenleme yoktur (!).
- Antidot olarak kullanılacak maddenin etkinliği bilimsel olarak kanıtlanmış olmalıdır.

Klinik ve antidot sorgulama

22

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- Antidotları üreten firmalar dünyada sınırlı sayıda,
 - Üretim kapasiteleri yıllık planlamayla sınırlı,
 - Belirlenmiş miktarın, belli merkezlerde stoklanmış olması gerekli.
-
- Sorumlu olan kurum 2001 yılından bu yana
RSHM Başkanlığı Zehir Danışma Merkezi

**UZEM**

Pestisit Zehirlenmeleri

Pestisitlerle zehirlenmeler genellikle kazaen olmaktadır. Genellikle de bu tür zehirlenmeler, gerek ilaçlama yaparken koruyucu önlemlerin alınmaması gerekse pestisitlerin kolay ulaşılabilir yerlerde bırakılması sonucunda, özellikle çocuklar başta olmak üzere, insanların yanlışlıkla bu ilaçlarla temas etmeleriyle olmaktadır. ([Devamı...](#))

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YEMEYİN**





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BİRİNCİ BASAMAĞA YÖNELİK ZEHİRLENMELER TANI ve TEDAVİ REHBERLERİ 2007



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BİRİNCİ BASAMAĞA YÖNELİK TANI VE TEDAVİ REHBERİ

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ULUSAL ZEHİR DANIŞMA MERKEZİ ANTİDOT LİSTESİ

Sıra	ANTİDOT ETKEN MADDE	ANTİDOTUN ADI	AMBALAJ TİPİ	BİRİM DEĞERİ	ENDİKASYONU
1	4-metil pirazol (Fomepizol sulfat)	FOMEPIZOL	5 amp / kutu	100 mg / 20 ml	Etilen glikol ve Methanol zehirlenmeleri
2	Botulismus Polivalan Antiserum (A-B-E)	BOTULİSMUS ANTİTOKSİN	250 ml şişe	Tip A 750 IU/ml Tip B 500 IU/ml Tip E 50 IU/ml	Botulismus vakaları için Antitoksin
3	Calcium Ededate sodyum	CALCIUM EDEDATE DE SODIUM % 5	10 amp / kutu	500 mg / 10 ml	Kurşun zehirlenmeleri
4	Di cobalt EDTA	KELOCYANOR % 1,5	6 amp / kutu	300 mg / 20 ml	Siyanür zehirlenmeleri
5	Digoksin İmmün Fab	DİGİFAB	1 vial / kutu	40 mg / vial	Digoksin zehirlenmeleri
6	Dimercaprol	B.A.L.	12 amp / kutu	200 mg / 2 ml	Ağır metal şelatörü
7	DMPS	DİMAVAL	20 cap / kutu	100 mg kapsül	Ağır metal şelatörü (Hg)
8	D-penisilamin	METACAPTASE	100 cap / kutu	150 mg kapsül	Ağır metal şelatörü (Pb, Cu)
9	Etil Alkol	ETİL ALKOL % 10	500 ml şişe	500 ml şişe	Etilen glikol ve Methanol zehirlenmeleri
10	Hydroxocobalamin	CYANO KİT 2,5 g	2 vial / kutu	2,5 gr vial	Siyanür zehirlenmeleri
11	Metilen Mavisi	METİLEN MAVİSİ % 1	1 flakon	20 ml / flakon	Methemoglobinemi yapan zehirlenmeler
12	Physostigmine	ANTİCHOLİUM	5 amp / kutu	2 mg / 5 ml	Antikolinerjik zehirlenmeler
13	Pralidoksim	CONTRATHİON	10 flakon / kutu	200 mg / flakon	Organik fosfor zehirlenmeleri
14	Silibinin	LEGALON-SİL	4 flakon / kutu	350 mg / flakon	Mantar zehirlenmeleri
15	Succimer (DMSA)	SUCCİCAPTAL	15 cap / kutu	200 mg / kapsül	Ağır metal şelatörü (Hg)

Kamu Hizmet Standartları

Misyonumuz

Vizyonumuz

Değerlerimiz

TÜRK HİJYEN ve
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BaşkanlığıCemal Gürsel Cad. No: 18
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Faks: (0312) 458 24 08

RSHM Kod	UBB Kod		Satış Fiyatı TL
131.100		ANTİDOT	
131.103	15.03.01.12.02.13.01	Botulismus Polivalan Antiserumu (Tip A. B ve E)	9.770,00
131.105	15.03.01.12.02.14.01	Calcium Edtate De Sodium	450,00
131.106	15.03.01.12.02.15.01	Dicobalt EDTA (Kelocyanor) (6 Amp/kutu)	445,00
131.107	15.03.01.12.02.16.01	Digifab (Digoxin İmmune Fab) 40 mg vial	1.450,00
131.112	15.03.01.12.02.17.01	Dimercaprol (BAL) (British Anti-Lewisite) 12 amp/kutu	380,00
131.115	15.03.01.12.02.18.01	DMPS (Dimercaptopropane-1-sulfonate) (Dimaval) 5 amp/kutu	629,00
131.116	15.03.01.12.02.18.02	DMPS (Dimercaptopropane-1-sulfonate) (Dimaval) 20 cap/kutu	325,00
131.118	15.03.01.12.02.26.01	DMSA (Dimercaptosuccinic acid) Succimer 15 cap/kutu	487,00
131.121	15.03.01.12.02.19.02	D-Penicilamin (Metacaptase) 300mg/100 cap. Kutu	353,00
131.122	15.03.01.12.02.19.01	D-Penicilamin (Metacaptase) 150mg/100 cap. Kutu	60,00
131.124	15.03.01.12.02.20.01	Etil Alkol (%10) 500cc şişe	16,00
131.127	15.03.01.12.02.21.01	Fomepizol (4-methypyrazole) (5 Amp/Kutu=)	3.029,00
131.130	15.03.01.12.02.23.01	Metilen Mavis (10 mL) %1	2,50
131.133	15.03.01.12.02.22.01	Physostigmin salicylat (5 Amp)	231,00
131.136	15.03.01.12.02.24.01	2- PAM (200 mg 10 Amp)Pralidoksime tuzları	76,33
131.139	15.03.01.12.02.12.01	Silibinin (4 Vialık kit)	2.430,00
131.142	15.03.01.12.02.25.01	Siyanür Antidot Kiti (Amil nitrit. Sodyum nitrit. Sodyum thiosülfat) (bir hastalık kit)	3.228,00

Popüler/Güncel Antidotlar-1

Antidote	Primary Indication by Substance	Dose and Administration
High dose insulin euglycemic therapy (HIE)	Severe calcium channel blocker poisoning	• Bolus of Regular Insulin 1U/kg followed by infusion at 0.5–1.0 U/kg/h. Give 25 gm (50 cc of D50W) initially and monitor glucose frequently to prevent hypoglycemia. Monitor serum potassium and replace as needed to avoid hypokalemia.

The proposed mechanism by which HIET reverses hemodynamic collapse is through direct metabolic effects on myocardial cells.^{6–8} It is hypothesized that in a state of shock, myocytes switch from the utilization of free fatty acids to glucose in order to meet metabolic demands. CCBs induce a state of hypoinsulinemia, preventing the uptake of glucose by myocytes and causing a loss of inotropy, decreased peripheral vascular resistance, and shock.^{6–8} High doses of insulin might therefore be able to reverse these metabolic derangements.

Popüler/Güncel Antidotlar-1

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HIGH-DOSE INSULIN EUGLYCEMIC THERAPY FOR THE TREATMENT OF CALCIUM CHANNEL BLOCKER OVERDOSE

It should not be overlooked, however, that there are many published case reports demonstrating the failure of HIET to reverse CCB-induced hemodynamic collapse. Some of these reports have in common the late initiation of HIET, after the development of severe symptoms,^{16–18} and may indicate that HIET should be considered early in severe CCB toxicity rather than as a therapy of “last resort.”

Popüler/Güncel Antidotlar-2

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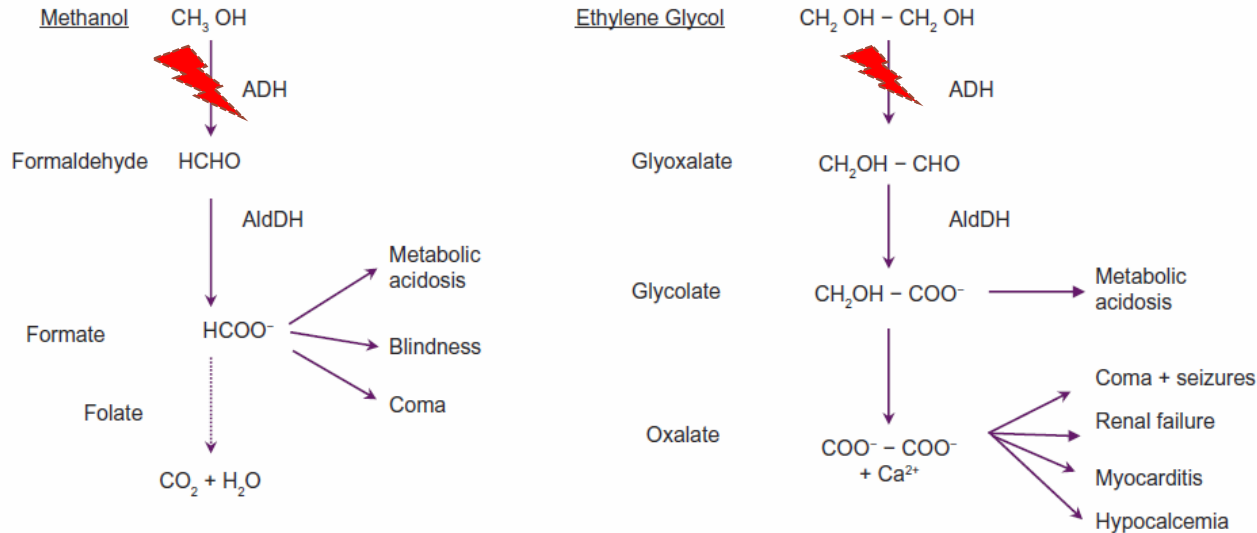
Antidote	Primary Indication by Substance	Dose and Administration
Intravenous lipid emulsion (Intralipid)	Lipophilic cardiotoxic agents	• 1.5 mL/kg of 20% intralipid as an initial bolus followed by 0.25 mL/kg/min for 30–60 min. • Depending upon response, bolus could be repeated 1-2 times and infusion rate increased.

Several mechanisms of action have been suggested. One theory is that ILE acts as a “lipid sink,” expanding the lipid compartment within the intravascular space, and sequestering lipid-soluble drugs from the tissues. The success of ILE in the treatment of poisoning by lipid-soluble drugs such as bupivacaine, propranolol, and verapamil supports this theory. Another explanation suggests that its efficacy is related to metabolic effects in the myocardium, specifically its ability to enhance fatty acid intracellular transport in myocardial cells.¹⁹

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Fomepizole

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New Developments in Antidotes

Nicole L. Ries, PharmD^{a,*},
Richard C. Dart, MD, PhD^{a,b}

^aRocky Mountain Poison and Drug Center, Denver Health, Denver, CO, USA

^bUniversity of Colorado Health Sciences Center, Denver, CO, USA

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Fomepizole and ethanol are two effective antidotes for the treatment of ethylene glycol (EG) and methanol poisoning [9]. Both fomepizole and ethanol are inhibitors of the alcohol dehydrogenase (ADH) enzyme; fomepizole is a more potent ADH inhibitor than ethanol [10,11]. In addition, fomepizole is eliminated more slowly than ethanol, has more predictable pharmacokinetics, is easier to administer, and requires less laboratory monitoring [12,13].

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REVIEW

Treatment of patients with ethylene glycol or methanol poisoning: focus on fomepizole

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Dosage and available formulations

Fomepizole is available in 1.5 mL vials containing 1 g/mL [16]. Intravenous (IV) administration is the recommended route, but fomepizole may be administered orally if IV access cannot be obtained [17]. Fomepizole is administered as an IV loading dose of 15 mg/kg, diluted in at least 100 mL of normal saline, or 5% dextrose in water, and infused over 30 minutes. The maintenance dose is 10 mg/kg IV every 12 hours for four doses. Administration beyond the initial five doses (48 hours) should be given at 15 mg/kg IV every 12 hours [16]. The recommended increase in the maintenance dose after the initial five doses is due to the autoinduction of fomepizole metabolism [18–21]. Fomepizole as monotherapy for EG or methanol intoxication should be given until the patient is asymptomatic, and the EG or methanol serum concentration is below 20 mg/dL [16].

TEŞEKKÜRLER...

