

# ZEHİRLENMELERDE ANTİDOT TEDAVİSİ

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Doç Dr Özlem GÜNEYSEL

Dr Lütfi Kırdar Kartal EAH  
Acil Tıp Kliniği

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 soil”,
- “Ermeni kütüğü”





## 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
  - Pralidoxime (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](http://www.sciencedirect.com)



Toxicology 233 (2007) 13–19

**TOXICOLOGY**

[www.elsevier.com/locate/toxicol](http://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*

Received 13 November 2006; received in revised form 22 November 2006; accepted 24 November 2006

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

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<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.

## YELLOWTOX

[World directory of poisons centres](#)

**Read a day in the life of a Poisons Information Centre pharmacist**  
[Full text](#)

## RELATED WEB SITES

[IPCS INCHEM](#)

**IFCS Forum V**  
Essential tools for chemical safety  
[Full text](#)

**INTERNATIONAL PROGRAMME  
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

16

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





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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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| Glucagon                                                   | Beta-blockers                                                           |
| Hydroxocobalamin                                           | Cyanide                                                                 |
| Methionine                                                 | Paracetamol                                                             |
| 4-Methylpyrazole                                           | Methanol; ethylene glycol                                               |
| Methylthioninium chloride (methylene blue)                 | Methaemoglobinaemia                                                     |
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| Naloxone                                                   | Opiates                                                                 |
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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.

# 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

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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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*"Hiçbir Lezzet Ölecek Kadar Güzel Değildir"*

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YEMEYİN**





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BİRİNCİ BASAMAĞA YÖNELİK  
**ZEHİRLENMELER  
TANI ve TEDAVİ  
REHBERLERİ  
2007**



REFİK SAYDAM HIFZISSIHHA MERKEZİ BAŞKANLIĞI - HIFZISSIHHA MEKTEBİ MÜDÜRLÜĞÜ

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## ZEHİRLENME TEDAVİSİNDE KULLANILAN İLAÇLAR ve ÖZGÜL ANTİDOTLAR - 2007

### BİRİNCİ BASAMAĞA YÖNELİK TANI VE TEDAVİ REHBERİ

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# RSHM’de bulunan Antidotlar

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## 1. Pralidoksim

Ülkemizde yaygın olarak kullanılan tarım ilaçlarından organofosforlu insektisitler ve özel koşullarda karbamatlı insektisitlerle meydana gelen zehirlenmelerde kullanılmaktadır.

## 2. Botulismus Antitoksini

## 3. BAL (Dimercaprol)

Kurşun, antimon, bizmut, arsenik, altın, krom, bakır, nikel, çinko ve civa gibi metallerle meydana gelen zehirlenmelerde

## 4. Succimer

Civa, kadmiyum, kurşun zehirlenmelerinde,

## 5. Kelocyanor (Dikobalt EDTA)

Siyanür zehirlenmesinde;

## Kamu Hizmet Standartları

## Misyonumuz

## Vizyonumuz

## Değerlerimiz

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Hıfzıssıhha Merkezi  
BaşkanlığıCemal Gürsel Cad. No: 18  
Tel : (0312) 458 20 00  
Faks: (0312) 458 24 08

| RSHM Kod | UBB Kod              |                                                                                            | Satış Fiyatı<br>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<br>amp/kutu                                 | 380,00             |
| 131.115  | 15.03.01.12.02.18.01 | DMPS (Dimercaptopropane-1-sulfonate)<br>(Dimaval) 5 amp/kutu                               | 629,00             |
| 131.116  | 15.03.01.12.02.18.02 | DMPS (Dimercaptopropane-1-sulfonate)<br>(Dimaval) 20 cap/kutu                              | 325,00             |
| 131.118  | 15.03.01.12.02.26.01 | DMSA (Dimercaptosuccinic acid) Succimer 15<br>cap/kutu                                     | 487,00             |
| 131.121  | 15.03.01.12.02.19.02 | D-Penicilamin (Metacaptase) 300mg/100 cap.<br>Kutu                                         | 353,00             |
| 131.122  | 15.03.01.12.02.19.01 | D-Penicilamin (Metacaptase) 150mg/100 cap.<br>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.<br>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 | <ul style="list-style-type: none"><li>• 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.</li></ul> |

The proposed mechanism by which HIET reverses hemodynamic collapse is through direct metabolic effects on myocardial cells.<sup>6–8</sup> 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.<sup>6–8</sup> High doses of insulin might therefore be able to reverse these metabolic derangements.

\*Emerg Med Clin North Am. 2010 Feb;28(1):149-61, ix.

# 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,<sup>16–18</sup> 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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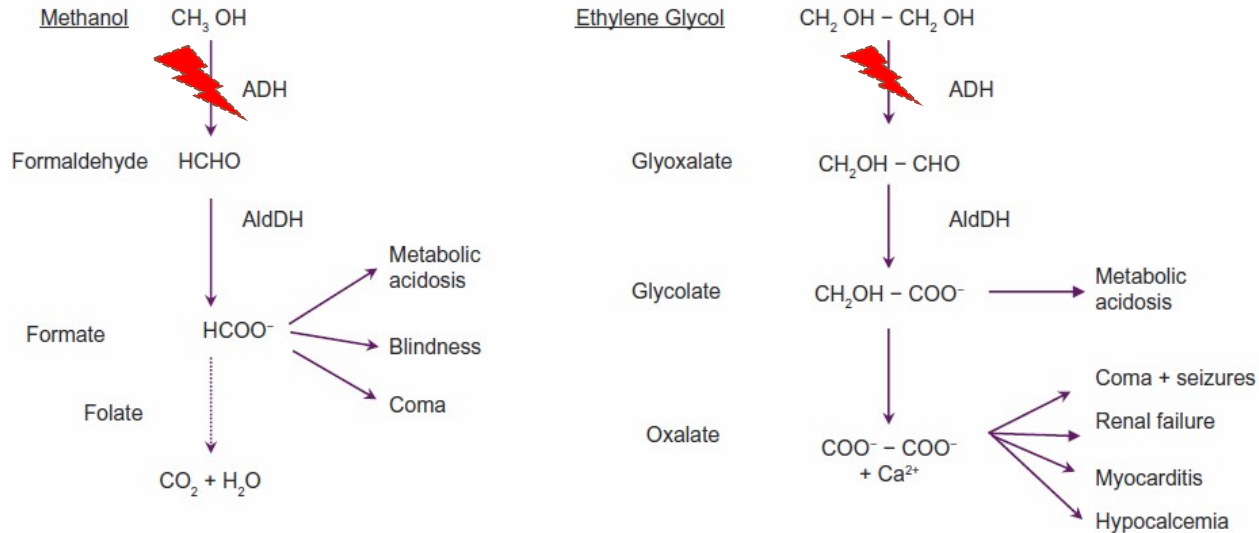
| Antidote                                | Primary Indication by Substance | Dose and Administration                                                                                                                                                                                                                       |
|-----------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intravenous lipid emulsion (Intralipid) | Lipophilic cardiotoxic agents   | <ul style="list-style-type: none"><li>• 1.5 mL/kg of 20% intralipid as an initial bolus followed by 0.25 mL/kg/min for 30–60 min.</li><li>• Depending upon response, bolus could be repeated 1-2 times and infusion rate increased.</li></ul> |

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.<sup>19</sup>

# Popüler/Güncel Antidotlar-3

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## Fomepizole



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## New Developments in Antidotes

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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

Open Access Emergency Medicine 2010:2

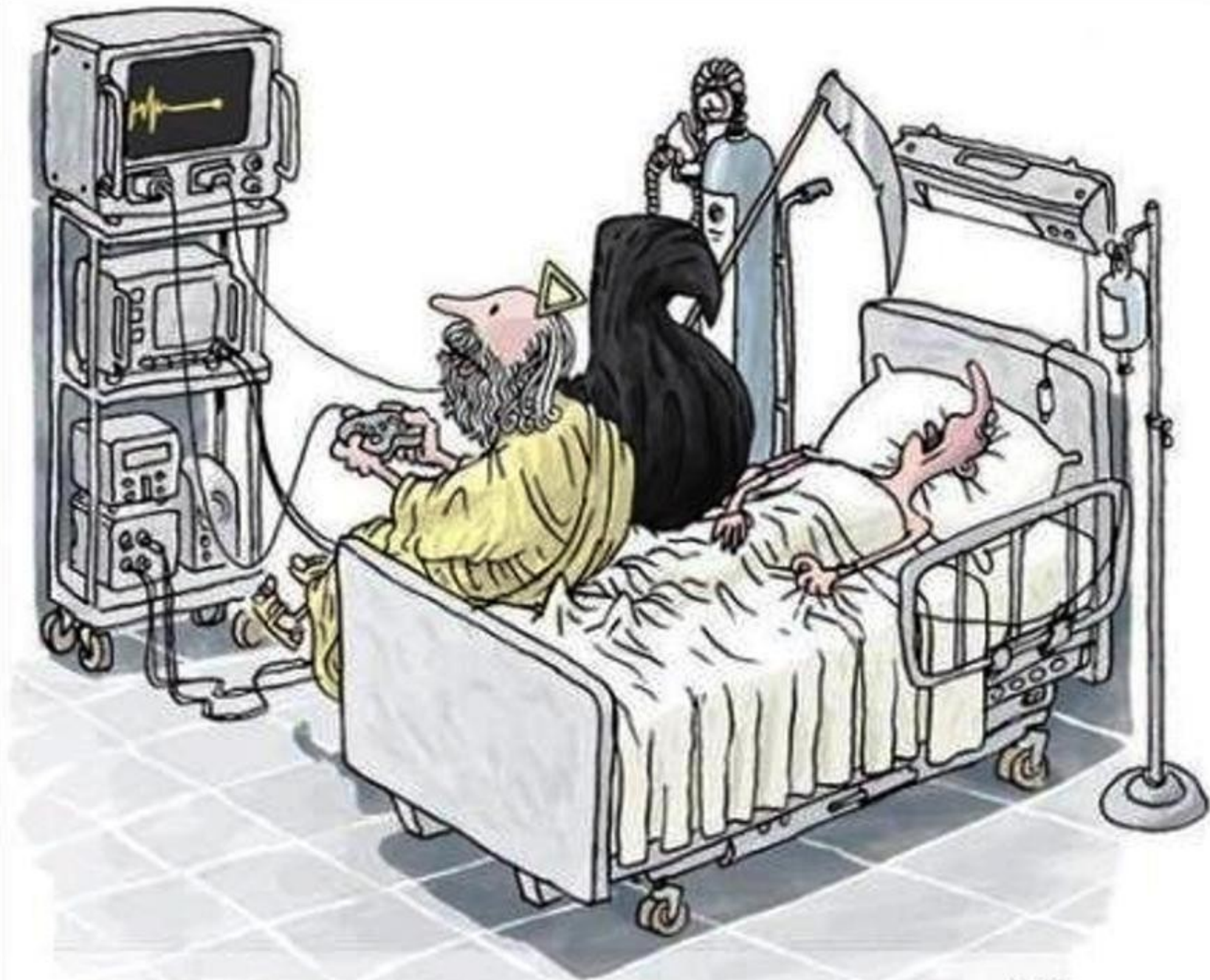
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# Popüler/Güncel Antidotlar-3

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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].



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