Güncel Antidotlar ve Kullanım Alanları

Doç Dr Halil KAYA

Harran Üniversitesi Tıp Fakültesi

Acil Tıp AD

Sunu planı

- Antidot nedir, tarihte antidotlar
- Günümüzde antidotlar
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- Güncel antidotlar
- Hastane stoklarında bulundurulması gereken antidotlar
- Özet

Antidot

- Zehirin toksikokinetik ve toksikodinamiğini değiştirebilen,
- Kullanımı güvenli,
- Zehirlenen kişide dikkate değer yararlı etkileri olan madde

- Halk arasında **panzehir,**
- Farmakolog ve toksikologlar arasında ise **yetim ilaç,**

Antidot

- Hayatı tehdit eden zehirlenmelerde genellikle tek doz olarak,

- Gerekli durumlarda ise tekrarlayan dozlarda uygulanır.

Antidot

Antidot

- Zehiri etkisizleştiren
- Zehirin etkisini önleyen
- Zehirin etkisini azaltan madde

İdeal antidot

- Hiçbir toksik etkiye sahip olmamalı,
- Zehirlenme etkenine özgül olmalı,
- Ucuz ve kolay ulaşılabilir olmalı

Tarihte Antidotlar

- Yunan mitolojisinde şifa tanrıçası **Panacea**'nın her hastalığı iyileştiren bir iksire sahip olduğu söylenir.
- İnsanlar her çeşit toksine karşı kişiyi koruyabilen ve **tiryak** denen evrensel antidotun peşindedir.
- İlk Tiryak formülü, Kos adasında Eskülap tapınağında taş üzerinde kayıtlıdır.
- Anadolunun antidotu **" Mesir Macunu"** 41 değişik baharattan oluşur.

Antidotlar yetim ilaçtır

Üretim maliyetleri yüksek

İlaç firmalarının ilgisi az

Yetim ilaç (Orphan drug)

Klinik araştırma oldukça zor

İhtiyaca bağlı olarak üretimi gerçekleştiren ülkeden ithal edilir

Günümüzde antidotlar

- Genellikle vaka serileri,
- Hayvan çalışmaları,
- Deneysel çalışmalar yapılmaktadır.

➢ Klinik araştırmalar ise nadirdir.

EK – 1: UZEM ANTİDOT LİSTESİ

ULUSAL ZEHİR DANIŞMA MERKEZİ ANTİDOT LİSTESİ					
Sıra	ANTİDOT ETKEN MADDE	ANTİDOTUN ADI	AMBALAJ TİPİ	BİRİM DEĞERİ	ENDİKASYONU
1	4-metil pirazol (Fomepizol sulfat)	FOMEPİZOL	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)

Antidot

- Antidotlarla ilgili bilgiler, uluslararası organizasyonlarca yayınlanır:
  - WHO (World Health Organisation)
  - UNEP (United Nations Environment Programme)
  - ILO (International Labour Organisation)

- Türkiye'de 2001 yılından bu yana sorumlu olan kurum **RSHM Başkanlığı Zehir Danışma Merkezi**

Yeni antidot

- Çoğu antidot bir **“model bileşik”** üzerinde yapılan çalışmalar ile keşfedilmiş.

- Terapötik indeksi en iyi olan bileşik antidot olarak kullanıma girmektedir.

- Yeni bir antidotun klinikte kullanıma girmesinde en zor kısım, **bu model bileşiğin** bulunmasıdır.

Bateman N, Marrs TC. Antidotal studies. In: Ballantyne B, Marrs TC, Syversen T (eds). General and applied toxicology. 2nd ed. New York: Grove’s Dictionaries, 2000; 425-37.

Yeni antidot?

Etik (onam) zorluk olması

Zehirlenmeler ilaç firmalarının ilgisini çekecek kadar fazla değil

Antidotlar yetim ilaçlardır.. (orphan drug)

Bu nedenle yeni antidot az/yok

Antidot sınıflandırma

4 ana gruptur:

a-Kimyasal antagonistler

b-Fizyolojik antagonistler

c-Farmakolojik antagonistler

d-Metabolizma düzeyindeki antagonistler

Kimyasal antagonistler

Vücutta zehirle kimyasal kompleks yapar. Bu yolla zehiri inaktive eder. Bazen de oluşan kompleks aracılığı ile itrahı artırır.

İlaç	Antidot
Civa, arsenik, bizmut, kadmiyum	Dimerkaprol
Kurşun	Kalsiyum disodyum EDTA, penisilamin, dimerkaprol
Demir	Desferrioksamin (deferoksamin)
Bakır ve altın bileşikleri	Penisilamin
Heparin	Protamin sülfat
Asetaminofen (parasetamol)	N-asetilsistein
Siyanürler ve sodyum nitroprusiyat	Hidroksikobalamin

Fizyolojik Antagonistler

Zehirlenme etkeni tarafından etkilenen yapılar üzerinde zıt yönde etki yapan maddelerdir.

İlaç	Antidot
Konvülsiyon yapıcılar	Diazepam, barbitüratlar
Vazokonstriktör ilaçlar	Nitritler ve diğer vazodilatörler
Amfetaminler	Klorpromazin ve türevleri
İzoniazid	Pridoxin

Farmakolojik antagonistler

Zehirlenme etkeninin etkilediği reseptörü bloke ederek antidotal etkinlik yaparlar.

İlaç	Antidot
Narkotik analjezikler	Naloksan
Muskarinik ilaçlar ve antikolinesterazlar	Atropin
Atropin	Fizostigmin
Histamin	Antihistaminikler

Metabolizma düzeyindeki antagonistler

İlaç	Antidot
Oral antikoagülanlar	K1- vit
CO	Saf Oksijen
Methotreksat	Folinik asit
Metil alkol ve etilen glikol	Etanol
Siyanür	Na-tiyosülfat
Asetaminofen	NAC
Organofosfatlar	PAM, Obidoksim
Methemoglobinemi	Metilen mavisi

Güncel Antidotlar

- 1-İV Lipid Tedavisi
- 2-İnsülin - glukoz (Hiperinsülinemi-öglisemi tdv)
- 3-Organofosfat (OP) zehirlenmelerinde yeni antidotlar
- 4-Etil Alkol zehirlenmesinde **zitramin**
- 5-Siyanür zehirlenmelerinde yeni antidotlar
- 6-Mantar zehirlenmelerinde silibinin

Güncel Antidotlar

İntravenöz Lipit Emülsiyon Tedavisi

- Lokal anestezikler (özellikle bupivakain)
- Antidepresanlar (Amitriptilin, sitalopram, bupropion ve venlafaksin)
- Antipsikotikler (ketiapin ve olanzapin)
- Kardiyovasküler ilaçlar (Ca kanal blokerleri, beta blokerler ve antiaritmikler)

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HIET (Hiperinsülinemi öglisemi ted)

- Ciddi anstabil KKB ve BB zehirlenmeleri tedavisinde etkin
- İnsülin kalbi metabolik olarak hücre düzeyinde korur.
- Kalp hücreleri içine glukoz reuptakini arttırır.
- İnotropik etkiyi arttırır.
- NO üzerinden VD etki ile vasküler rezistansı azaltarak kardiyak outputu arttırır.

Agarwal A, et al. Hyperinsulinemia euglycemia therapy for calcium channel blocker overdose: a case report. Tex Heart Inst J. 2012;39(4):575-578.
Engebretsen KM, et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila). 2011;49(4):277-283.

Güncel Antidotlar

HIET (Hiperinsülinemi öglisemi ted)

- Eğer bir hasta sıvı, atropin, Ca ve glukagon uygulanmasına rağmen hipotansif ve bradikardikse HIET uygulanmalı
- Maximum ins dozu tanımlanmamış.
- **Yükleme** dozu 0.5 - 1 U/kg bolus regüler insülin ve 25 gr Dx
- **İnfüzyon** dozu 0.5 - 1 U/kg/sa regüler ins ve 0.5 g/kg/sa Dx
- Kan şekeri ve K yakın takip edilmeli

Boyer EW, Duic PA, Evans A. Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. *Pediatr Emerg Care.* 2002; 18:36–7.
Yuan TH, Kerns WP II, Tomaszewski CA et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *J Toxicol Clin Toxicol.* 1999; 37:463–74.

Güncel Antidotlar

Organo P-Yeni antidotlar

- a-Yeni oksimler
- b-Magnezyum Sülfat
- c-NaHCO3
- d-Antioksidanlar
- e-Anisodamin

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Oximlerin rolü tam olarak açık değildir. Bunlar sadece spesifik pestisitlere veya orta düzeyli zehirlenmelere yararlı olabilir.

Management of acute organophosphorus pesticide poisoning

Michael Eddleston, Nick A Buckley, Peter Eyer, Andrew H Dawson

Organophosphorus pesticide self-poisoning is an important clinical problem in rural regions of the developing world, and kills an estimated 200 000 people every year. Unintentional poisoning kills far fewer people but is a problem in places where highly toxic organophosphorus pesticides are available. Medical management is difficult, with case fatality generally more than 15%. We describe the limited evidence that can guide therapy and the factors that should be considered when designing further clinical studies. 50 years after first use, we still do not know how the core treatments—atropine, oximes, and diazepam—should best be given. Important constraints in the collection of useful data have included the late recognition of great variability in activity and action of the individual pesticides, and the care needed cholinesterase assays for results to be comparable between studies. However, consensus suggests that early resuscitation with atropine, oxygen, respiratory support, and fluids is needed to improve oxygen delivery to tissues. The role of oximes is not completely clear; they might benefit only patients poisoned by specific pesticides or patients with moderate poisoning. Small studies suggest benefit from new treatments such as magnesium sulphate, but much larger trials are needed. Gastric lavage could have a role but should only be undertaken once the patient is stable. Randomised controlled trials are underway in rural Asia to assess the effectiveness of these therapies. However, some organophosphorus pesticides might prove very difficult to treat with current therapies, such that bans on particular pesticides could be the only method to substantially reduce the case fatality after poisoning. Improved medical management of organophosphorus poisoning should result in a reduction in worldwide deaths from suicide.

Lancet 2008; 371: 597–607
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See Comment page 538
See Articles page 579
See Case Report page 622

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Organophosphorus pesticide self-poisoning is a major clinical and public-health problem across much of rural Asia.[1–3] Of the estimated 500 000 deaths from self-harm in the region each year,[4] about 60% are due to pesticide poisoning.[1] Many studies estimate that organophosphorus

Unfortunately, these hospitals are frequently not adequately staffed or equipped to deal with these very sick patients—intensive care beds and ventilators are in short supply—so even unconscious patients are managed on open wards (figure 1). Furthermore, the

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Moshiri et al. DARU Journal of Pharmaceutical Sciences 2012, 20:81
http://www.darujps.com/content/20/1/81

DARU Journal of Pharmaceutical Sciences

REVIEW ARTICLE Open Access

Advances in toxicology and medical treatment of chemical warfare nerve agents

Mohammd Moshiri[1], Emadodin Darchini-Maragheh[2,3] and Mahdi Balali-Mood[2,4*]

Abstract

Organophosphorous (OP) Nerve agents (NAs) are known as the deadliest chemical warfare agents. They are divided into two classes of G and V agents. Most of them are liquid at room temperature. NAs chemical structures and mechanisms of actions are similar to OP pesticides, but their toxicities are higher than these compounds. The main mechanism of action is irreversible inhibition of Acetyl Choline Esterase (AChE) resulting in accumulation of toxic levels of acetylcholine (ACh) at the synaptic junctions and thus induces muscarinic and nicotinic receptors stimulation. However, other mechanisms have recently been described. Central nervous system (CNS) depression particularly on respiratory and vasomotor centers may induce respiratory failure and cardiac arrest. Intermediate syndrome after NAs exposure is less common than OP pesticides poisoning. There are four approaches to detect exposure to NAs in biological samples: (I) AChE activity measurement, (II) Determination of hydrolysis products in plasma and urine, (III) Fluoride reactivation of phosphylated binding sites and (IV) Mass spectrometric determination of cholinesterase adducts. The clinical manifestations are similar to OP pesticides poisoning, but with more severity and fatalities. The management should be started as soon as possible. The victims should immediately be removed from the field and treatment is commenced with auto-injector antidotes (atropine and oximes) such as MARK I kit. A 0.5% hypochlorite solution as well as novel products like M291 Resin kit, G117H and Phosphotriesterase isolated from soil bacterias, are now available for decontamination of NAs. Atropine and oximes are the well known antidotes that should be infused as clinically indicated. However, some new adjuvant and additional treatment such as magnesium sulfate, sodium bicarbonate, gacyclidine, benactyzine, tezampanel, hemoperfusion, antioxidants and bioscavengers have recently been used for OP NAs poisoning.

Keywords: Nerve agents, Chemical warfare agent, Organophosphorous compounds, Pesticides, Sodium bicarbonate, Magnesium sulfate, Iran

Güncel Antidotlar

Table 3 New recommended treatments for organophosphorous nerve agents

Category	Drug	Benefit
Anti-NMDA and anti-glutamate drugs	Gacyclidine	Early administration could prevent the mortality
	Tezampanel	It reduced the length of status epilepticus induced by soman exposure. Useful in protection of neuropathy induced by soman
	Ketamine	Could stop seizure and reduced seizure-related brain damage, protection against OP nerve agent poisoning of peripheral and CNS AChE
	Huperzine A	Useful effects on seizures and status epilepticus prevention in post-exposure,
Magnesium Sulphate:		Administration in the first day decreases hospitalization period and improve outcomes in patients
Antioxidants:	Vitamin E	Therapeutic effects in OPs induced oxidative stress
Bioscavengers:	BChE purified from human plasma (HuBChE)	Therapeutic blood concentration of BChE can be kept for at least 4 days after a single dose administration
	Fetal bovine serum AChE (FBSAChE)	Protected against multiple LD50s of organophosphate NAs
	Fresh frozen plasma (FFP)	No significant effect

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OP–Yeni Oksimler

- Son yıllarda yapılan in-vivo ve in-vitro çalışmalarda K-oksimlerin AChE reaktivasyonunda PAM'dan daha etkili olduğu görülmüş.

- Ancak yapılan Cochrane analizinde yeterli kanıt olmadığı ve özellikle insanları kapsayan daha fazla çalışma yapılması gerektiği vurgulandı.

Buckley NA, Eddleston M, Li Y, Bevan M, Robertson J. Oximes for acute organophosphate pesticide poisoning. Cochrane Database Syst Rev 2011;2:CD005085.

Güncel Antidotlar

OP-MgSO4

- MgSO4 ligand kapılı Ca kanallarını bloke eder, presinaptik terminalden Ach salınımı azalması ile sonuçlanır.

*Singh G, Avasthi G, Khurana D, Whig J, Mahajan R. Neurophysiological monitoring of pharmacological manipulation in acute organophosphate poisoning. The eff ects of pralidoxime, magnesium sulphate and pancuronium. *Electroencephalogr Clin Neurophysiol 1998; 107: 140–48.*

** Pajoumand A, Shadnia A, Rezaie A, Abdi M, Abdollahi M. Benefi ts of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides. *Hum Exp Toxicol 2004;* ***23: 565–69.***

Güncel Antidotlar

OP–MgSO4

- 4 gr Mg sülfat eğer hastanın ilk hastaneye başvurduğu gün verilirse hastanede yatış süresini azaltır ve iyileşme oranını arttırır
- Kalsiyum kanal blokajı yaparak asetil kolin salınımını azaltır.
- NMDA reseptör aktivasyonu sağlayarak SSS'nin aşırı uyarılmasını ve kas fasikülasyonlarını engeller.
- Atropin ihtiyacını azaltır
- Rutin kullanıma girmesi için daha fazla çalışma gerekli

Eddleston M, Buckley NA, Eyer P, Dawson AH: Management of acute organophosphorus pesticide poisoning. Lancet 2008, 371:597–607

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informa
healthcare

CRITICAL CARE

Phase II study of magnesium sulfate in acute organophosphate pesticide poisoning

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Background. Acute organophosphorus (OP) poisoning is relatively common and a major cause of death from poisoning in developing countries. Magnesium has been shown to be of benefit in animal models. *Methods.* We conducted a phase II study of bolus doses of (MgSO4) in 50 patients with acute organophosphate poisoning. Patients eligible for inclusion had ingested OP and had cholinergic symptoms consistent with moderate or severe poisoning. All patients received standard care of atropinization titrated to control muscarinic symptoms and pralidoxime. The trial was run in 4 sequential groups of patients. Participants in each group received a different total dose of MgSO4 (20%) administered as intermittent bolus doses infused over 10–15 min or placebo. There was one control patient for every 4 patients who received MgSO4. Group A (16 patients) received a total of 4 gm MgSO4 as a single bolus, group B (8 patients) received 8 gm (in two 4 gm doses q4H), group C (8 patients) received 12 gm (in three 4 gm doses q4H) group D (8 patients) received 16 gm (in four 4 gm doses q4H) and control (10 patients) received placebo). Patients were closely monitored for any adverse reaction like significant clinical neuromuscular disturbance and respiratory depression. *Results.* No adverse reactions to magnesium were observed. The 24 hour urinary magnesium concentration were statistically different between 16 gm (234.74 ± 74.18 mg/dl) and control (118.06 ± 30.76 mg/dl) ($p = 0.019$), while it was much lower than the 80% of the intravenous magnesium load. Six patients died in control group compared to 3 in 4 gm, 2 in 8 gm and 1 in 12 gm group. There was no mortality in 16 gm group. *Conclusion.* Magnesium was well tolerated in this study. Larger studies are required to examine for efficacy.

Keywords Other; Respiratory support; Metabolic Organophosphate; Magnesium

Güncel Antidotlar

OP-NaHCO3

- Alkalizasyon – hedef pH 7.45 ile 7.55 arası
- Asidoz varsa asidoz düzelene kadar ya da atropin ihtiyacı ortadan kalkıncaya dek 3–5 mg/kg/24 sa sürekli infüzyon
- Kardiyak toksisite gelişimini önler
- Atropinin etkinliğini arttırır.
- Oksimlerin biyoyararlanımını arttırır.
- Nörolojik fonksiyonlarda düzelme sağlar.

Balali-Mood M, Balali-Mood K: Neurotoxic disorders of organophosphorus compounds and their managements. Arch Iran Med 2008, 11:65–89.
Delfino RT, Ribeiro TS, Figueroa-Villar JD: Organophosphorus Compounds as Chemical Warfare Agents: a Review. J Braz Chem Soc 2009, 20:407–428.
Nurulain SN: Different approaches to acute organophosphorus poison treatment. J Pak Med Assoc 2012, 62:712–717.

Güncel Antidotlar

OP-NaHCO3

Sodium bicarbonate is sometimes used for treatment of organophosphorus poisoning in Brazil and Iran, in place of oximes. Increases in blood pH (up to 7·45–7·55) have been reported to improve outcome in dogs through an unknown mechanism; however, a Cochrane review concluded that insuffi cient evidence exists at present to establish whether sodium bicarbonate should be used in humans poisoned with organophosphorus.

Wong A, Sandron CA, Magalhaes AS, Rocha LCS. Comparative efficacy of pralidoxime vs sodium bicarbonate in rats and humans severely poisoned with O-P pesticide. J Toxicol Clin Toxicol 2000; ***38:****554–55.*

Balali-Mood M, Ayati MH, Ali-Akbarian H. Effect of high doses of sodium bicarbonate in acute organophosphorous pesticide poisoning. Clin Toxicol 2005; ***43: 571–74.***

Roberts D, Buckley NA. Alkalinisation for organophosphorus pesticide poisoning. Cochrane Database Syst Rev 2005; ***1: CD004897.***

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OP–Bioscavengers

- OP bileşiklerini stokiyometrik olarak bağlayanlar.
- AChE enzimini pseudo katalitik etki ile aktive edenler.
- OP hidrolaz ve OP anhidraz etkisi gösteren doğal katalitikler
- Taze donmuş plazma – AChE enzim seviyesini arttırır fakat klinik sonuçlarda bir değişiklik yok

-Ross MC, Broomfield CA, Cerasoli DM, Doctor BP, Lenz DE, Maxwell DM, Saxena A: Chapter 7: Nerve agent bioscavenger: Development of a new approach to protect against organophosphorus exposure. In Textbooks of military medicine ,medical aspects of chemical warfare. Edited by Lenhart MK, Tuorinsky SD. Washington, DC: The Office of the Surgeon General at TMM Publications; 2008:243–259.

- Pazooki S, Solhi H, Vishteh HR, Shadnia S, Beigi MJ: Effectiveness of fresh frozen plasma as supplementary treatment in organophosphate poisoning. Med J Malaysia 2011, 66:342–345.

- Pichamuthu K, Jerobin J, Nair A, John G, Kamalesh J, Thomas K, Jose A, Fleming JJ, Zachariah A, David SS, et al: Bioscavenger therapy for organophosphate poisoning - an open-labeled pilot randomized trial comparing fresh frozen plasma or albumin with saline in acute organophosphate poisoning in humans. Clin Toxicol (Phila) 2010, 48:813–819.

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OP-antioksidan

Expert Opin Drug Discov. 2013 Dec;8(12):1467-77. doi: 10.1517/17460441.2013.847920. Epub 2013 Oct 14.

Drug development for the management of organophosphorus poisoning.

Eisinghorst PW[1], Worek F, Thiermann H, Wille T.

⊕ Author information

Abstract

INTRODUCTION: The continuous application of organophosphate pesticides in developing countries, in addition to the remaining stock piles of chemical warfare nerve agents and their possible use is a significant threat to the public. Yet, today's options for a treatment of organophosphorus poisonings are still inadequate.

AREAS COVERED: This article provides a concise overview of current and future research trying to improve both prophylaxis and treatment of organophosphorus intoxications. The authors provide a summary of current oxime therapy and highlight several new concepts to overcome existing gaps. This overview of therapeutic options is accompanied by two sections on cyclodextrins, related compounds and bioscavengers, which may be used for either prophylaxis or treatment. For both groups, the authors review current drug design and screening approaches, the resulting developments and future challenges.

EXPERT OPINION: While the search for one multipotent oxime has been a fruitless endeavor, combination of multiple oximes with complemental and systemic reactivity appears as a valuable concept. Development of potential scavengers, be it cyclodextrins or bioscavengers, is still hampered by insufficient efficacy of these compounds. Future strategies will aim at improving their catalytic efficacy while minimizing immunogenicity.

Güncel Antidotlar

OP–E Vitamini

- OP zehirlenmeleri dokularda oksijen radikalleri birikimine yol açar.

- Ratlarda E vitamininin OP zehirlenmelerinin neden olduğu oksidatif hasarı önlediği görülmüş.

Balali-Mood M, Saber H: Recent advances in the treatment of organophosphorous poisonings. IJMS 2012, 37:74–91.
Balali-Mood M, Balali-Mood K, Hosseini Shirazi F: Recent advances in treatment of acute organophosphorous nerve agents poisoning. IJPR 2006, 5:79–87.

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Deneysel Akut Organik Fosfor Toksisitesi Tedavisine Eklenen E Vitaminin Olumlu Etkileri

The Favorable Effects of Vitamine E Added on Treatment of Experimental Acute Organic Phosphorus Toxicity

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ÖZET

Amaç

Pestisit zehirlenmelerinde reaktif oksijen türevlerinin artmış üretimine bağlı olarak oksidatif stres geliştiği bildirilmiştir. Doku ROS seviyeleri doku hasarının en önemli göstergelerindendir. Bu çalışmada, akut organofosfat (OF) zehirlenmesinde ek olarak kullanılacak E vitamininin tedavisinin kandaki ve karaciğer dokusundaki kolin esteraz (KE) ve malondialdehit (MDA) düzeyleri üzerine etkilerini araştırmak ve sadece antidot tedavisi verilen grup ile karşılaştırarak OF zehirlenmesi tedavisinde kullanılıp kullanılamayacağını belirlemektir.

Gereç ve Yöntem

Çalışmada 20 Yeni Zelanda cinsi tavşan randomize olarak sham (n=8), pralidoksim (PAM)+atropin (n=6) ve E vitamini (n=6) olarak 3 gruba ayrıldı. Her denekten toksisite öncesi plazma KE, serum ve eritrosit MDA değerlerini ölçmek için kan örnekleri alındıktan sonra orogastrik yoldan 50 mg/kg 2,2-diklorvinil dimetil fosfat verildi. PAM+atropin grubundaki deneklere 30 mg/kg IV bolus, ardından 15 mg/kg PAM ve 0.05 mg/kg atropin her 4 saatte İV verildi. E vitamini grubundaki deneklere benzer atropin ve PAM tedavisine ilaveten 250 mg/kg E vitamini tek doz İM uygulandı. Deneklerden tedavi başlatıldıktan sonra 12. ve 24. saatlerde kan örnekleri alındı. Tüm deneklerden aynı parametreleri değerlendirmek üzere karaciğer dokusu örnekleri alındı. Denekler yüksek dozda İV anestezik verilerek sakrifiye edildiler.

Bulgular

E vitamini grubunun eritrosit MDA'sı PAM+atropin grubundan anlamlı düşük (p=0.003) tespit edildi. E vitamini grubunun karaciğer dokusundaki KE düzeyi PAM+atropin grubundan anlamlı olarak yüksekti (p<0.001). E vitamini grubundaki tavşanların karaciğer doku MDA'sı PAM-atropin grubundan anlamlı olarak düşüktü (p<0.001).

Sonuç

Akut OF zehirlenmesinde antidot tedavisine eklenen E vitamini nin hem eritrosit ve karaciğer dokusu lipid peroksidasyonu üzerine hem de karaciğer dokusu KE aktivitesi üzerine iyileştirici etkisi vardır.

Anahtar sözcükler: E vitamini; kolinesteraz; malondialdehit; oksimler; or-

SUMMARY

Objectives

Oxidative stress by increased production of reactive oxygen species has been implicated in the toxicity of many pesticides. The tissue levels of ROS are one of the most important indicator of tissue injury. The aim of this study was to examine the effects of vitamin E treatment in acute organophosphate poisoning (AOP) on choline esterase (CE) and Malondialdehit (MDA) levels in the liver tissue and blood and to compare with antidote treatment.

Methods

Twenty New Zealand type rabbits were divided into randomly three groups as sham (n=8), pralidoxime (PAM)+atropine (n=6), and vitamin E (n=6). blood samples were taken from each test subjects to measure plasma CE, serum and erythrocyte MDA values before toxicity. 50 mg/kg 2,2-dichlorovinyl dimethyl phosphate were given to all subjects orogastrically. The PAM-atropine group were given 30 mg/kg IV bolus, then 15 mg/kg PAM and 0.05 mg/kg atropine IV every 4 hours. The vitamin E group received 250 mg/kg vitamin E single dose IM in addition to same atropine and PAM treatment. Blood samples were obtained from the all subjects in the 12th and 24th hours followed by the initiation of treatment. The liver tissue samples were obtained to evaluate in order to evaluate same parameters. The test subjects were sacrificed by high dose IV anesthesia.

Results

The erythrocyte MDA of vitamin E group was significantly lower than PAM-atropine group (p=0.003). Liver tissue CE level of vitamin E group was considerably higher than PAM-atropine group (p<0.001). Liver tissue MDA of vitamin E group was significantly lower than PAM-atropine group (p<0.001).

Conclusions

Included in the treatment of acute AOF toxicity, vitamin E has a curative effect on both erythrocyte and liver tissue lipid peroxidation and tissue CE activity.

Key words: *Vitamin E; cholinesterase; malondialdehyde; oxime; organophos-*

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Güncel Antidotlar

OP zehirlenmesinde TDP 'nin anlamlı etkisi bulunamadı

ORIGINAL ARTICLE

Effectiveness of Fresh Frozen Plasma as Supplementary Treatment in Organophosphate Poisoning

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SUMMARY

With the establishment of the inadequate efficiency of atropines and oximes in reducing morbidity and mortality of patients poisoned by organophosphates, more attention is given to using other methods such as Fresh Frozen Plasma (FFP) as a bioscavenger to mop up organophosphate toxins. This randomized clinical trial was conducted on 56 organophosphate poisoned patients who were randomly assigned to the FFP and control groups in order of admission. The routine treatment in both groups included atropine and, in moderate to severe cases of poisoning, pralidoxime. The FFP group received four packs of FFP as stat dose at the beginning of treatment. No significant difference was seen between the two groups on the atropine and pralidoxime dosage, hospitalization length and mortality. The present study showed that using four packs of FFP as stat dose at the onset of treatment had no significant effect on the clinical course of organophosphate poisoned patients.

KEY WORDS:
Organophosphate poisoning, FFP, Pralidoxime

Today, various methods have been attempted for the treatment of OP, including magnesium, hemoperfusion and alkalinisation (on humans) and N-acetyl cysteine (NAC), diazepam, clonidine and adenosine receptor antagonists (on animals) [16]. Since neutralizing toxins has always been a treatment goal, today bioscavengers have taken center stage to mop up free organophosphates. Such treatments may include the use of enzymes such as cholinesterase to block organophosphate compounds before reaching the toxicity threshold [17]. Therefore, in some human studies fresh frozen plasma (FFP) has been researched as a source for butyrylcholinesterase (BuChE) (psudo- or nonspecific cholinesterase) as a treatment method for OP [18-20]. Guven et al. were first to examine the effect of plasmaphresis using FFP on a patient poisoned by organophosphate [18] and then in a partially randomized controlled study, they investigated the efficacy of FFP on 12 patients and compared the results with those of 21 patients receiving conventional treatment [19]. However, another study in 2010 could not confirm the efficacy of FFP in OP patients [20]. Since using FFP is a new treatment method revealing contradictory results in previous few studies, the present preliminary study attempts to examine the effect of four packs of FFP as stat dose for

Pazooki S, Solhi H, Vishteh HR, Shadnia S, Beigi MJ: Effectiveness of fresh frozen plasma as supplementary treatment in organophosphate poisoning. Med J Malaysia 2011, 66:342–345.

Güncel Antidotlar

Anisodamin doğal bir atropin derivesi olup atropin ve scopolamine benzer.
64 OP zehirlenmesi vakası
Atropinizasyon başarısız olanlarda anisodamin verilmesi ile atropinizasyon süresi ve hastanede kalış süresi kısalmış.

Environ Toxicol Pharmacol. 2014 Mar;37(2):477-81. doi: 10.1016/j.etap.2013.12.016. Epub 2013 Dec 31.

Efficiency of anisodamine for organophosphorus-poisoned patients when atropinization cannot be achieved with high doses of atropine.

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Author information

Abstract

Poisoning by organophosphorus insecticides is a major global public health problem. Although atropine has been widely used to treat organophosphate (OP) poisoning, sometimes atropinization cannot be achieved, even with high doses of atropine. Hence, we aimed to assess the effect of anisodamine for organophosphorus poisoned patients for whom atropinization could not be achieved through high doses of atropine. In this study, sixty-four OP-poisoning patients, all of whom accepted routine treatments but who did not attain atropinization after high doses of atropine for 12 h, were enrolled. The result showed that the time to atropinization was 24.3±4.3 h in the anisodamine group, significantly shorter than in the atropine group (29.2±7.0 h, $p<0.05$); the hospital stay in the anisodamine group was 5.3±2.5 days, significantly shorter than the 6.9±2.3 days needed by the atropine group ($p<0.05$). We draw a conclusion that anisodamine can shorten the process of atropinization and hospital stay in organophosphorus poisoned patients for whom atropinization cannot be achieved with high doses of atropine.

KEYWORDS: Anisodamine; Atropine; Atropinization; Organophosphate poisoning

Güncel Antidotlar

Etanol X Zitramin

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Original Russian Text © M.G. Voronkov, G.G. Yushkov, A.V. Mashanov, A.Yu. Fedorin, M.M. Rasulov, V.V. Benemansky, G.A. Kuznetsova, 2013, published in Doklady Akademii Nauk, 2013, Vol. 451, No. 6, pp. 688–690.

BIOCHEMISTRY, BIOPHYSICS AND MOLECULAR BIOLOGY

Zitramin—A New Antidote for Acute Ethanol Intoxication

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The problem of alcohol abuse and ethanol intoxication of the Russian population requires the creation of effective antidotes. The effectiveness of some inorganic zinc compounds, in particular toxic $ZnSO_4$, is known [1]. We have studied the protective effect in acute ethanol intoxication of a new nontoxic (DL_{50} > 5000 mg/kg) organic zinc derivative—zinc diacetate complex with triethanolamine $(CH_3COO)_2Zn \cdot (HOCH_2CH_2)_3N$,1,1-diacetoxy-2,8,9-trihydrozincatrane (THZA, zitramin).

Experimental animals (outbred rats) were divided into three groups: (1) placebo control (animals received pure water from troughs), (2) positive control (animals were intragastrically administered with ethanol once at a dose of 12 g/kg), and (3) experimental group (animals were first intragastrically administered with ethanol once at a dose of 12 g/kg and then (in 30 min) intragastrically administered with THZA once at a dose of 4 mg/kg). Each group included 18 animals.

To determine the activity of alcohol dehydrogenase (ADH), substrates (blood and liver) was taken 30 min after the THZA administration to group 3 animals and 60 min after the ethanol administration in the in the positive control group and simultaneously in the placebo control group. The content of glucose (by the glucose oxidase method) and the activity of alanine aminotransferase (ALT, by the kinetic method) and alkaline phosphatase (ALP) in the blood serum and the activity of ADG in the liver tissue were determined in animals of all groups 60 min, 1 day, and 3 days after the beginning of the experiment.

In the study of the mechanism of action of THZA (Fig. 1). The activity of ADH in the control group (i.e., in the absence of ethanol and THZA) in the liver was very weak. A diffuse staining of dehydrogenases in the cytoplasm of hepatocytes was observed. Under the action of ethanol at a dose of 12 g/kg, a moderately severe activity of ADH in hepatocytes near the central veins was detected. In the case of the combined administration of ethanol and THZA, the activity of ADH was slightly higher than in the controls but significantly lower than under the effect of ethanol alone.

The time of the onset of alcohol-induced sleep in animals of groups 3 and 2 was almost the same (164 ± 31 and 154 ± 25 s, respectively), but the duration of this state in rats differed significantly (27300 ± 2500 and 43200 ± 1810 s, respectively). The alcohol-induced sleep of animals was accompanied by a significant decrease in the level of glycogen in the liver homogenates on day 1 after the administration of ethanol. In the group that was treated with THZA (0.004 mg/kg) after the administration of ethanol, the content of glycogen in the liver remained almost unchanged. On the third day of observations, it reached the values characteristic of the placebo control. The time course of the level of glucose in the blood serum was similar (Fig. 2).

The activity of ALP in the liver homogenate tended to increase mainly in group 2 and reached the maximum on day 1. In groups 2 and 3, ALP activity differed slightly. Even on day 3 after the ethanol administration, the activity of ALP in liver homogenates of the positive control group, in contrast to the experimental group, did not return to the level of the placebo control (Fig. 3).

Güncel Antidotlar

Etanol X Zitramin

- Zitramin bir organik çinko derivesi
- İntragastrik olarak etanol verilen ratlar üzerinde deneysel bir çalışma
- 18'er rattan oluşan 3 grup
- Zitraminin KCFT'nin düşürülmesinde etkili olduğu görülmüş
- Etanol intoksikasyonunda kullanılması için klinik çalışmalara ihtiyaç olduğu vurgulanmış.

Güncel Antidotlar

Siyanid antidotları

- Cobinamide ve sulfanegen kombinasyonu
- Nitrocobinamide

Güncel Antidotlar

Siyanid zehirlenmesinde cobinamide ve sulfanegen kombinasyonu umut vericidir.

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informa
healthcare

RESEARCH ARTICLE

The combination of cobinamide and sulfanegen is highly effective in mouse models of cyanide poisoning

ADRIANO CHAN[1,2], DAUNE L. CRANKSHAW[3], ALEXANDRE MONTEIL[3], STEVEN E. PATTERSON[3], HERBERT T. NAGASAWA[3], JACKIE E. BRIGGS[3], JOSEPH A. KOZOCAS[4], SARI B. MAHON[5], MATTHEW BRENNER[5], RENATE B. PILZ[1], TIMOTHY D. BIGBY[1,2], and GERRY R. BOSS[1]

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Güncel Antidotlar

Nitrocobinamide yeni bir siyanid antidotu olup kobinamid+sodyum nitrit birleşimi ile oluşur. Ve intramuskuler yolla verilebilir.

Abstract ▾ Send to: ▾

J Med Chem. 2015 Feb 26;58(4):1750-9. doi: 10.1021/jm501565k. Epub 2015 Feb 16.

Nitrocobinamide, a new cyanide antidote that can be administered by intramuscular injection.

Chan A[1], Jiang J, Fridman A, Guo LT, Shelton GD, Liu MT, Green C, Haushalter KJ, Patel HH, Lee J, Yoon D, Burney T, Mukai D, Mahon SB, Brenner M, Pilz RB, Boss GR.

⊕ Author information

Abstract

Currently available cyanide antidotes must be given by intravenous injection over 5-10 min, making them ill-suited for treating many people in the field, as could occur in a major fire, an industrial accident, or a terrorist attack. These scenarios call for a drug that can be given quickly, e.g., by intramuscular injection. We have shown that aquohydroxocobinamide is a potent cyanide antidote in animal models of cyanide poisoning, but it is unstable in solution and poorly absorbed after intramuscular injection. Here we show that adding sodium nitrite to cobinamide yields a stable derivative (referred to as nitrocobinamide) that rescues cyanide-poisoned mice and rabbits when given by intramuscular injection. We also show that the efficacy of nitrocobinamide is markedly enhanced by coadministering sodium thiosulfate (reducing the total injected volume), and we calculate that ~1.4 mL each of nitrocobinamide and sodium thiosulfate should rescue a human from a lethal cyanide exposure.

Güncel Antidotlar

Mantar - Silibinin

- Silibinin (Slymarin); suda çözünür silimarin derivesi olup amatoksinin hepatositler tarafından alımını engelleyen bir moleküldür.
- Klinik düzelme sağlamıştır.
- Silibininin ampirik olarak önerilen dozu **5 mg/kg** iv bolus sonrası **20 mg/kg/gün** sürekli infüzyon veya total **1400 mg/gün** şeklindedir.
- Tedavi 3–4 gün boyunca sürdürülmelidir.

Güncel Antidotlar

604 amanita şüpheli hastanın 367'si retrospektif incelenmiş.
118'ine sadece silibinin, 249'una ise silibinin+penisilin verilmiş.
Sadece silibinin verilenlerde silibinin+penisilin verilenlere göre daha az sayıda ölüm ve transplantasyon

Dtsch Med Wochenschr. 2008 Oct;133(44):2261-7. doi: 10.1055/s-0028-1091268. Epub 2008 Oct 22.

[Amanita poisoning--comparison of silibinin with a combination of silibinin and penicillin].

[Article in German]

Ganzert M[1], Felgenhauer N, Schuster T, Eyer F, Gourdin C, Zilker T.

Author information

Abstract

BACKGROUND AND AIMS: Current treatment of amatoxin poisoning includes the administration of silibinin and penicillin in combination or silibinin alone. The aim of this study was to compare both therapeutic regimes.

PATIENTS AND METHODS: Of 604 patients with the suspected diagnosis of amatoxin poisoning 367 were retrospectively analysed: 118 patients had received silibinin alone and 249 patients silibinin in combination with penicillin. Logistic regression analyses were applied to investigate the efficacy of both therapeutic regimens by comparing death and liver transplantation rates. A potentially independent effect on outcome of age, sex, year of treatment, latency period of symptoms and start of silibinin therapy was taken into account.

RESULTS: In the group who had received the combination of silibinin and penicillin 8.8% died or underwent liver transplantation compared to 5.1% in the group of those who had received silibinin alone. The risk of death or organ transplantation was thus reduced by nearly 40% in the latter group (adjusted odds ratio: 0.58; 95% CI: 0.21-1.57; p=0.28). A longer latency period (< or =12h vs. >12h) was associated with a significant reduction of this risk (adjusted OR.: 6.10; 95% CI:1.77-21.3; p=0.004). A later start of silibinin therapy (>24h vs. < or = 24h) was associated with a tendency toward an increased frequency of death or organ transplantation (adjusted OR.: 3.0; 95% CI: 0.96-9.20; p=0.059).

CONCLUSIONS: A lower death and transplantation rate was observed in the silibinin treatment group than in group treated with silibinin combined with penicillin. However, this difference was not statistically significant. The high risk ratio relating to the time-dependent effect of silibinin suggests its efficaciousness in the treatment of amatoxin poisoning. The latency period was assessed as an independent prognostic factor.

Güncel Antidotlar

Yeni Kuşak Antikoagülanların Antidotu?

- Son yıllarda kullanıma giren yeni antikoagülanlar: **dabigatran, rivaroksaban, apiksaban, edoksaban**
- Bazı spesifik antidotlar geliştirilme aşamasında

Güncel Antidotlar

Yeni Kuşak Antikoagülanların Antidotu?

- **Idarucizumab:** Bir Fab fragmanı ve *dabigatrana spesifik bir antidot.*
- **Andexanet alfa:** Enzimatik olarak inaktive edilmiş faktör Xa'nın kesilmiş formu olup, faktör Xa inhibitörlerine (*rivaroksaban, apiksaban ve edoksaban) bağlanarak etkilerini geri döndürür*
- **Aripazine :** Küçük bir sentetik molekül olup (~500 Da) *oral dabigatran, apiksaban, rivaroksaban yanında subkutan fondaparinuks ve in vivo LMWH etkilerini geri döndürür.*

Güncel Antidotlar

Yeni Kuşak Antikoagülanların Antidotu?

Abstract ▾ Send to: ▾

J Thromb Thrombolysis. 2015 Apr;39(3):395-402. doi: 10.1007/s11239-015-1167-9.

Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents.

Siegal DM[1].

⊕ Author information

Abstract

Target-specific oral anticoagulants (TSOACs) dabigatran, rivaroxaban and apixaban are approved for the prevention and treatment of thromboembolism in several clinical settings. Bleeding is the major complication of anticoagulant therapy, including TSOACs, and anticoagulant reversal strategies are highly desired for the management of anticoagulant-associated major bleeding in addition to maximum supportive care and procedural/surgical intervention. Unlike VKAs for which vitamin K and coagulation factor replacement with prothrombin complex concentrate (PCC) can restore hemostasis, there are no clinically available agents proven to reverse TSOAC anticoagulant effect and ameliorate TSOAC-related major bleeding. This narrative review critically evaluates the evidence for TSOAC reversal using non-specific reversal agents PCC, activated PCC (APCC) and recombinant activated factor VII (rVIIa) which have been assessed primarily using in vitro experiments, animal models and healthy human volunteers. Aripazine is a novel agent undergoing clinical development for non-specific anticoagulant reversal, including TSOACs. Data are presented regarding specific reversal agents idarucizumab (dabigatran) and andexanet alfa (oral factor Xa inhibitors) currently being evaluated in clinical trials. A practical approach to management of patients with TSOAC-associated bleeding is also provided. There is an urgent need for clinical studies that evaluate the efficacy and safety of reversal strategies for TSOAC-related major bleeding with assessment of clinical outcomes such as bleeding and mortality.

Hastane stoklarında hangi antidotlar?

- Hastanede bulunması önerilen antidot miktarı **“minimum stok”** ile ifade edilmektedir.
- Minimum stok; 70 kg’lık bir ya da iki hastanın kabulünden itibaren ilk dört saatlik tedaviyi karşılayacak dozdur.
- 24 antidot göz önüne alınmış,
- 12 antidotun acil servis stoklarında olması gerektiği vurgulanmış.

Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Dart RC et al. Ann Emerg Med 2009;54:386

Hastane stoklarında hangi antidotlar?

Acil servis stoklarında olması gereken antidotlar

Atropin	**Metilen mavisi**
Kalsiyum glukonat	Naloksan,
Siyanid antidot kiti veya hidroksikobalamin	Fizostigmin,
Digoksin immün Fab	Pridoksin
Flumazenil,	Sodyum bikarbonat
Glukagon	

Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Dart RC et al. Ann Emerg Med 2009;54:386

Hastane stoklarında hangi antidotlar?

1 saat içinde ulaşılması gerekenler

Asetilsistein	**Dimerkaprol**
Polivalan Yılan antivenomu	Etanol veya fomepizol
Polivalan immün Fab	Oktreotid
Mercan yılanı antivenomu	Potasyum iyodid
Desferroksamin	Pralidoksim

Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Dart RC et al. Ann Emerg Med 2009;54:386

Hastane stoklarında hangi antidotlar?

- Flumazenil ve fizostigmin acil servis stoklarında olmalı.

- Crotalide antivenin çok pahalı, bölgesel riskler göz önüne alınmalı

Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Dart RC et al. Ann Emerg Med 2009;54:386

Özet

- Zehirlenmelerde antidotların rolü önemlidir.
- Akılcı kullanımı mortalite ve morbiditeyi engeller.
- Akut zehirlenme olgularında antidotun zamanında verilmemesi hasta kaybına neden olabilir.
- Antidotlar yeterli miktarda stoklanmalı.
- Antidotu olmayan zehirlenmeler için yeni antidotlar geliştirilmelidir.

TEŞEKKÜRLER