ANTİDOT TEDAVİLERİ VE YENİ YAKLAŞIMLAR

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ANTİDOT

- Bir başka ilaç veya toksinin toksikokinetiğini veya toksikodinamiğini degiştirerek (fizyolojik, mekanik, kimyasal) etkisini azaltan veya geri çevirebilen (nötralize eden) ilaç, şelatör veya kimyasal madde.
- WHO'a göre: Spesifik bir xenobiotiğin toksik etkisini veya etkilerini nötralize etmek, ortadan kaldırmak için kullanılan tedavi edici maddeler.

- Antididonai: Yunanca 'karşı verilen' anlamında
- Antik Yunanlarda İ.Ö. 185-135 Nicander Kolofana 'Aleksifarmaka' adlı kitabında antidotlardan bahsetmiştir.
- pontius-sky (opium, bazı bitkiler ve kurutulup toz haline getirimiş yılan dahil 54 farklı maddeden oluşan madde)
- Daha sonra sadece analjezik ve sedatif etkisi olmasına rağmen teryak adı verilen madde yüzyıllarca antidot olarak kullanıldı.
- I.Ö. 72-23 yıllarında Pliny II tarafından süt üniversal antidot olarak tanımlandı.
- Ibni Sina (Avicenna 980-1037) bitkisel, hayvansal ve mineral kaynaklı çoğu antidot olarak kullanılan 812 ilaç tanımladı.
- 1846 'da Garrod strychnine, aconitine, hydrocyanic acid ve bir çok potent toksin ile birlikte aktif kömür verilen hayvanların toksik etkiden korunabildiğini buldu.
- Aktif Kömür: Üniversal Antidot

INDICATION: MOST POISONS

ANTIDOTE: ACTIVATED CHARCOAL

INDICATION: PARACETAMOL, CARBON TETRACHLORIDE

ANTIDOTE: ACETYLCYSTEINE

INDICATION: ORGANOPHOSPHATES AND CARBAMATE POISONING

ANTIDOTE: ATROPINE

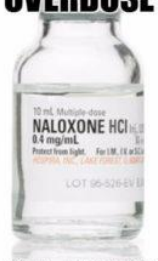
INDICATION: BENZODIAZEPINE OVERDOSE

ANTIDOTE: FLUMAZENIL

INDICATION: BETA BLOCKERS, CALCIUM CHANNEL BLOCKERS AND HYPOGLYCEMIC TOXICITY

ANTIDOTE: GLUCAGON

INDICATION: OPIOID OVERDOSE



ANTIDOTE: NALOXONE

INDICATION: ORGANOPHOSPHOROUS INSECTICIDES

ANTIDOTE: PRALIDOXIME

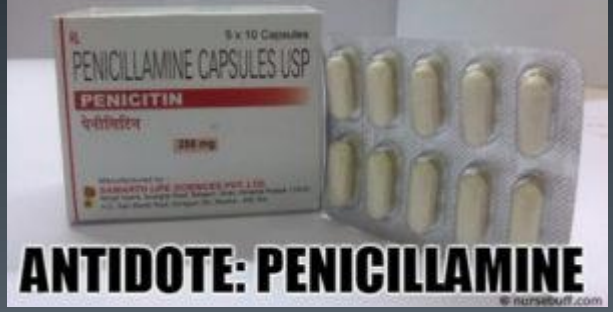
INDICATION: ANTI-COAGULANT POISONING

ANTIDOTE: PHYTOMENADIONE (VITAMIN K)

INDICATION: HEPARIN POISONING

ANTIDOTE: PROTAMINE SULFATE

INDICATION: LEAD, COPPER AND ARSENIC POISONING



ANTIDOTE: PENICILLAMINE

INDICATION: AMATOXIN POISONING

ANTIDOTE: SILIBININ

İDEAL ANTİDOT

- Toksine spesifik
- Yan etkisi az
- Uygulanması kolay
- Kolay temin edilebilir
- Ucuz

MEKANİK ETKİLİ ANTİDOTLAR

- Toksinin emilimini engelleyen antidotlar!
- Absorbsiyon - Aktif kömür
- Kaplama - Süt ve yumurta karışımı
- Çözünme - Karbolik asidin %10 alkol veya glisin ile çözünmesi

AKTİF KÖMÜR

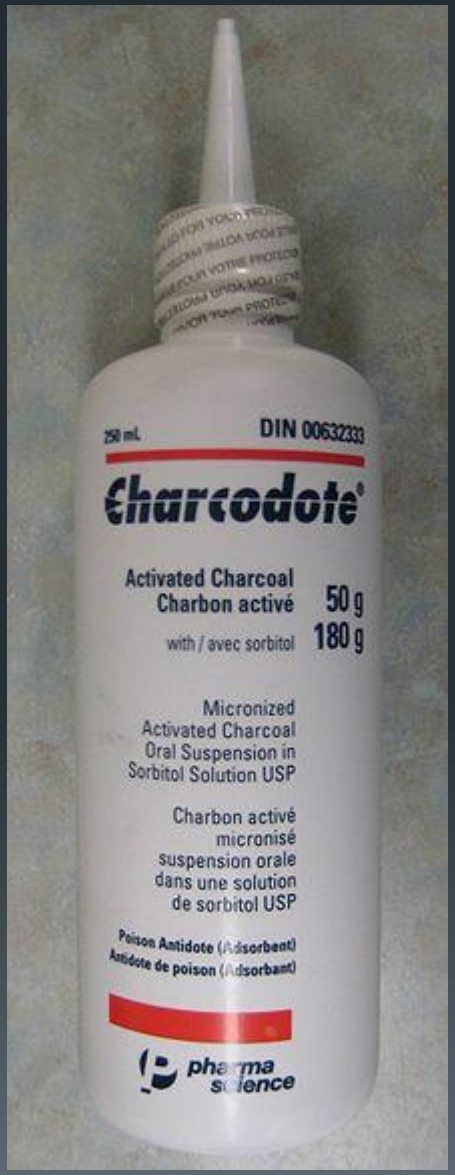
- Yüksek karbon içeren maddelerin (örneğin tahta) çok yüksek ısıda yakılması ile elde edilen siyah, kokusuz toz.
- Kömür, daha sonra, kömür parçacıkları üzerinde yüzey alanını ve mevcut bağlama alanlarını artırmak için çok sayıda delik ve aralık oluşturan özel bir işlemle "aktive" edilir.
- Bir çay kaşığı aktif kömür yaklaşık bir futbol sahası büyüklüğünde yüzey alanına sahiptir.
- Bağırsakta ilaç-toksinleri adsorbe ederek vücuda alınmasını engeller.
- Tek doz kullanımda bir yaş altında 10-25 gr (0.5-1 gr/kg), 1-12 yaş arası 25-50 gr (0.5-1 gr/kg), 12 yaş üzerinde 25-100 gr (1-2 gr/kg)
- Multi doz kullanımda 13 yaşa kadar 10-25 gr ilk dozu takiben 2-4 saatte bir 1-2 gr/kg, 13 yaş ve üzerinde 50-100 gr ilk dozu takiben saat başı 12.5 gr veya 2 saatte bir 25 gr veya 4 saatte bir 50 gr

LIST OF ADSORBED TOXINS

Agents WELL Adsorbed by Activated Charcoal				Agents POORLY Adsorbed by Activated Charcoal
Acetylsalicylic Acid	Chloroquines	Indomethacin &	Phenylbutazone	Cyanide
Aflatoxin	& Primaquine	other NSAIDs	Phenylpropanolamine	Ethanol
Amphetamines	Cimetidine	Kerosene, Benzene,	Piroxicam	Ethylene Glycol
Antidepressants	Dapsone	Dichloroethane	Phenol Syrup of	Iron
Antiepileptics	DDT	Malathion & other Pesticides	IPECAC constituents	Isopropanol
Antihistamines	Dextropropoxyphene	Meprobamate	Quinidine & Quinine	Lithium
Aspirin/	& other opioids	Nefopam	Strychnine	Methanol
Other Salicylates	Digitalis	Methotrexate	Tetracyclines	Strong Mineral Acids & Alkali
Atropine	DIQUAT &	Mexiletine	Theophylline	
Barbiturates	other Herbicides	NSAIDS	Torbutamide,	
Benzodiazepines	Glycosides Disopyramide	(e.g. Tolfenamin Acid)	Chlorpropamide	
Beta-blockers	Ergot Alkaloids	*Paracetamol	Carbutamide,	
Biphenyls	Furosemide	PARAQUAT	Tolazamide	
Carbamazepine	Glibenclamide & Glipizide Glutethimide	Polychlorinated Phenothiazines		

* *In cases of severe paracetamol poisoning,concurrent intravenenous antidote (N-acetylcysteine)administration and oral Norit Carbomix is recommended.*

Multi Doz Aktif Kömürün Etkili Olduğu İlaçlar/Toksinler		
Carbamazepine	Dapsone	Digitoxine
Disopyramide	Nadolol	Phenobarbital
Phenylbutazone	Pheytoine	Piroxicam
Quinine	Salicylates	Sotalol
Teophylline	Uzun salınımlı ilaçlar	Enterik kaplı ilaçlar



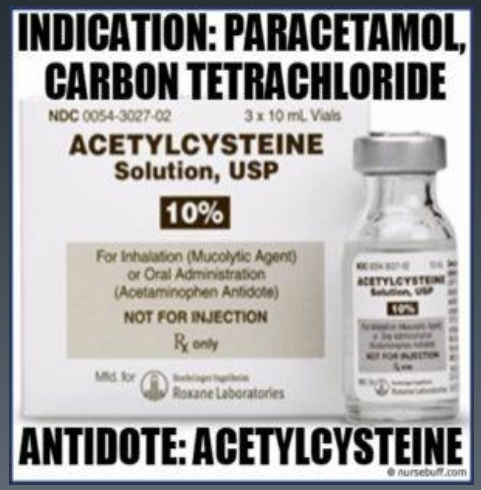
KİMYASAL ANTİDOTLAR

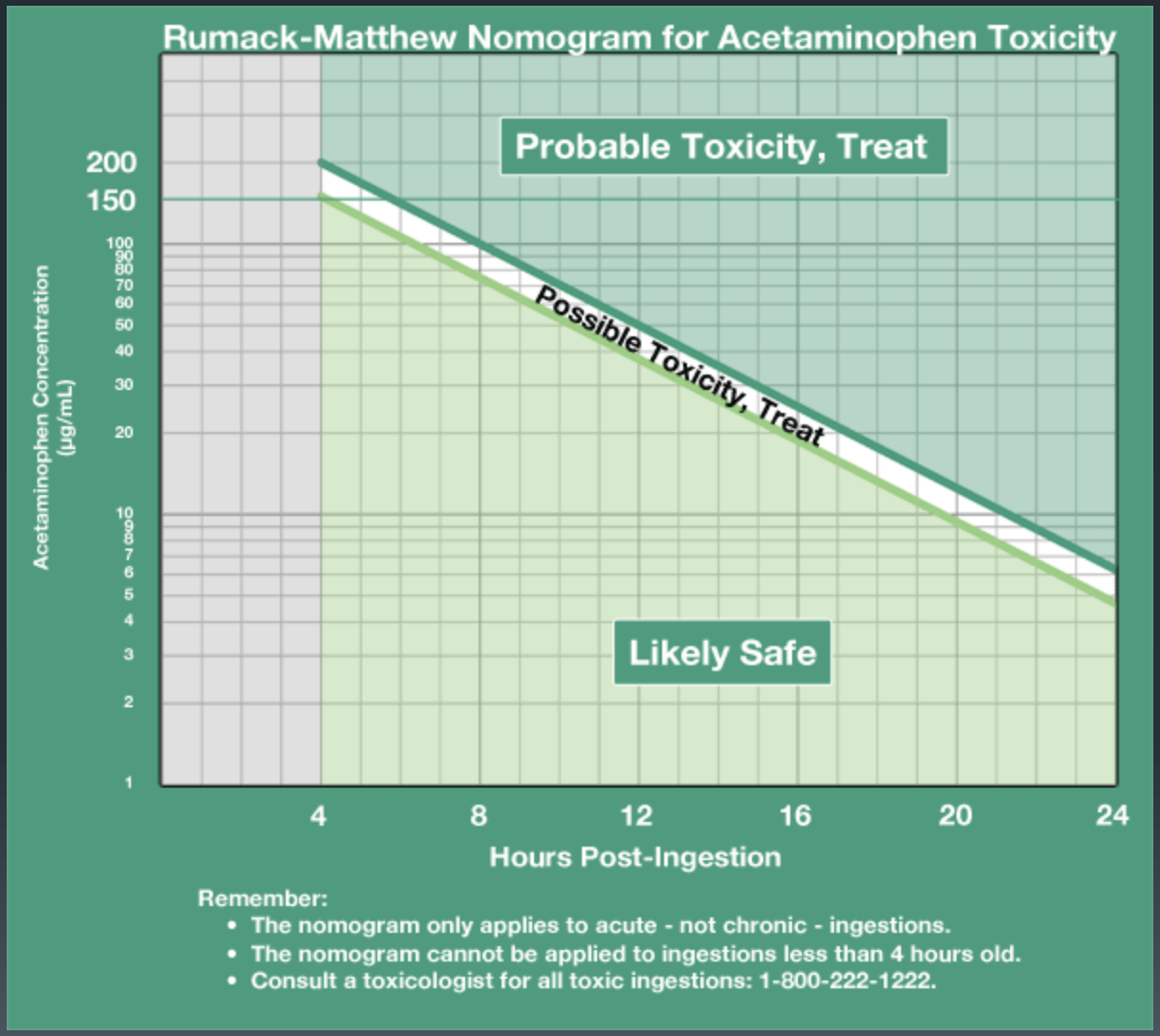
- Toksinin kimyasal yapısını değiştirerek nontoksik bileşenlere çevirirler.
- Siyanid, Na-thiosulphate tarafından nontoksik thiocyanate'a çevrilir.

TOKSİN/İLAÇ	ANTİDOT
Asetaminofen (APAP)-Parasetamol	N-Asetilsistein (NAC)
Heparin	Protamin Sülfat
Civa, kadmiyum, bizmut, arsenik	Dimerkaprol
Sodyum nitroprussid, siyanür	Hidroksikobalamin
Kurşun	Penisilamin, dimerkaprol, Ca-disodyum EDTA
Altın, bakır	Penisilamin
Demir	Deferoksamin

NAC

- Toksik doz parasetamol alımlarından sonra ilk 8 saatte başlanması hepatotoksisite riskinin azaltılması için hayatidir.
- Toksisite sonrası ilk 4 saat içinde gelen vakalarda parasetamol düzeyi belirlenir. NAC tedavisine başlamak için Rumack-Matthew Nomogramı kullanılır. Kan parasetamol düzeyi tedavi hattının üzerinde ise (150 mg/ml) NAC başlanır.
- Dört saatten sonra 24 saat içinde başvuran hastalarda 4.7 mg/ml üzerinde kan düzeylerinde NAC başlanır.
- Kan parasetamol düzeyi tespit edilemiyorsa tüm toksik doz alımlarda.




Rumack-Matthew Nomogram for Acetaminophen Toxicity
Probable Toxicity, Treat
Possible Toxicity, Treat
Likely Safe
Acetaminophen Concentration (µg/mL)
200
150
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
4
8
12
16
20
24
Hours Post-Ingestion
Remember:
• The nomogram only applies to acute - not chronic - ingestions.
• The nomogram cannot be applied to ingestions less than 4 hours old.
• Consult a toxicologist for all toxic ingestions: 1-800-222-1222.

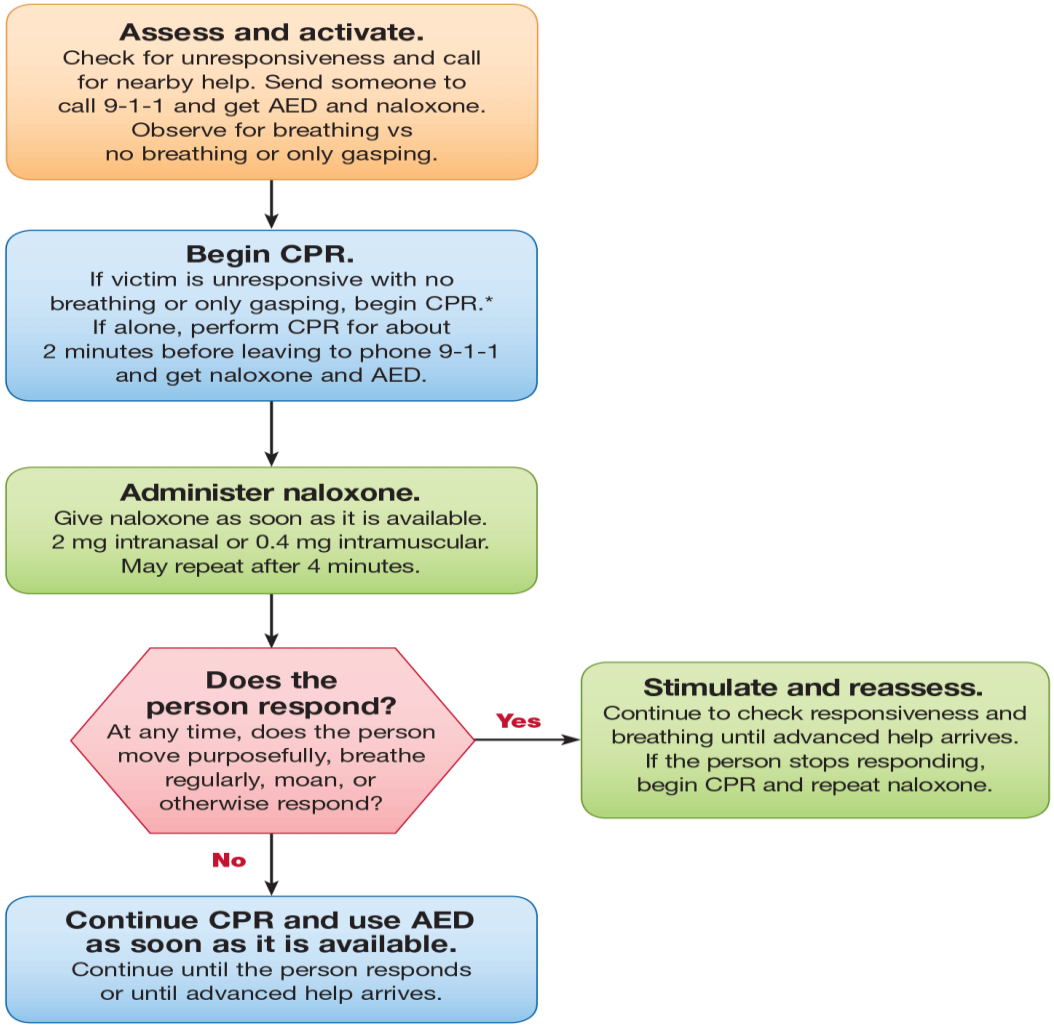
NAC

- Oral: 140 mg/kg yükleme, sonra 70 mg/kg toplam 17 doz (72 saatte)
- İV: 150 mg/kg 200 ml %5 dekstroz içinde 1 saatte yükleme, sonraki 4 saatte 500 ml %5 dekstroz içinde 50 mg/kg, sonraki 16 saatte 1000 ml %5 dekstroz içinde 100 mg/kg

FARMAKOLOJİK ANTİDOTLAR

- Toksik metabolitlerin oluşması engelleyen antidotlar (Etilen glikol – Etil alkol, 4 metil pirazol)
- Toksik maddenin tam veya hızlı eliminasyonunu sağlayan antidotlar
- Reseptör için toksin ile kompetitif-nonkompetitif yarışan antidotlar (Naloxon – opioidler, flumazenil –benzodiazepinler, organofosfatlar ve diğer parasempatomimetikler – atropin, kalsiyum glukonat – kalsiyum kanal blokerları, PAM - organofosfat)
- Toksik etkiden sorumlu reseptörü bloke eden antidotlar: Atropin organofosfat toksisitesinde kolinerjik sinapslarda ve nöromüsküler kavşakta asetikolini bloke eder.
- Normal fonksiyonun restore edilmesine yardım eden antidotlar: NAC - parasetamol

Opioid-Associated Life-Threatening Emergency (Adult) Algorithm—New 2015



*CPR technique based on rescuer's level of training.

Maternal Cardiac Arrest

First Responder

- Activate maternal cardiac arrest team
- Document time of onset of maternal cardiac arrest
- Place the patient supine
- Start chest compressions as per BLS algorithm; place hands slightly higher on sternum than usual

Subsequent Responders

Maternal Interventions

Treat per BLS and ACLS Algorithms

- Do not delay defibrillation
- Give typical ACLS drugs and doses
- Ventilate with 100% oxygen
- Monitor waveform capnography and CPR quality
- Provide post–cardiac arrest care as appropriate

Maternal Modifications

- Start IV above the diaphragm
- Assess for hypovolemia and give fluid bolus when required
- Anticipate difficult airway; experienced provider preferred for advanced airway placement
- If patient receiving IV/IO magnesium prearrest, stop magnesium and give IV/IO calcium chloride 10 mL in 10% solution, or calcium gluconate 30 mL in 10% solution
- Continue all maternal resuscitative interventions (CPR, positioning, defibrillation, drugs, and fluids) during and after cesarean section

Obstetric Interventions for Patient With an Obviously Gravid Uterus*

- Perform manual left uterine displacement (LUD)—displace uterus to the patient's left to relieve aortocaval compression
- Remove both internal and external fetal monitors if present

Obstetric and neonatal teams should immediately prepare for possible emergency cesarean section

- If no ROSC by 4 minutes of resuscitative efforts, consider performing immediate emergency cesarean section
- Aim for delivery within 5 minutes of onset of resuscitative efforts

*An obviously gravid uterus is a uterus that is deemed clinically to be sufficiently large to cause aortocaval compression

Search for and Treat Possible Contributing Factors (BEAU-CHOPS)

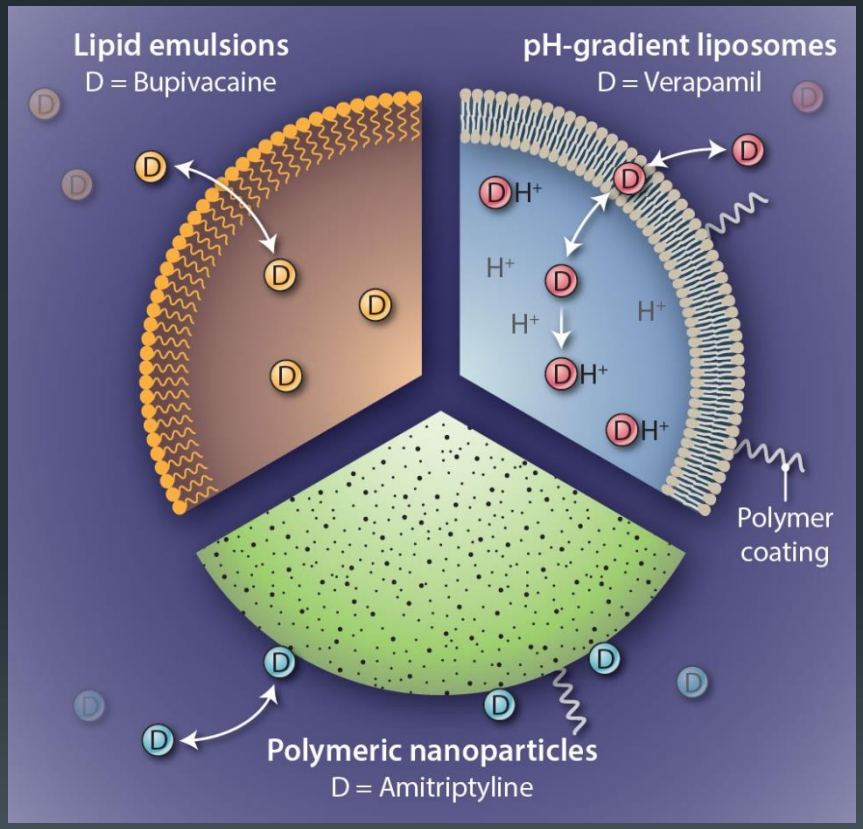
Bleeding/DIC
Embolism: coronary/pulmonary/amniotic fluid embolism
Anesthetic complications
Uterine atony
Cardiac disease (MI/ischemia/aortic dissection/cardiomyopathy)
Hypertension/preeclampsia/eclampsia
Other: differential diagnosis of standard ACLS guidelines
Placenta abruptio/previa
Sepsis

No.	Antidotes	Intoxicated agents	Recommended classification*
1	Activated charcoal	Most therapeutic drugs (for absorbable poisons)	IIA
2	Atropine	Organophosphate, carbamate etc.	IA
3	Beta-blockers	Beta-adrenergic agonists	IA
4	Calcium gluconate or other calcium salts	Hydrofluoric acid, fluorides, oxalates	IA
5	Diazepam	Organophosphorus compounds	IIA
6	Digoxin-specific fab antibody fragments	Digoxin, digitoxin, Natural cardioactive steroids	IA
7	Ethanol	Toxic alcohols (methanol, ethylene glycol etc.)	IA
8	Flumazenil	Benzodiazepine	IIA
9	Folinic acid	Methotrexate	IA
10	Fomepizole	Toxic alcohols (methanol, ethylene glycol etc.)	IA
11	Glucagon	Beta-blocker	IA
12	Glucose (hypertonic)	Insulin	IA
13	*N*-acetylcysteine	Acetaminophen	IA
14	Neostigmine	Nondepolarizing neuromuscular blocking agents	IIA
15	Pralidoxime	Organophosphorus compounds	IA
16	Sodium bicarbonate	Tricyclic antidepressant	IA
17†	Hydroxocobalamin	Cyanide	IA
18†	Amyl nitrite	Cyanide poisoning	IA
18†	Sodium nitrite	Cyanide	IA
18†	Sodium thiosulfate	Cyanide, nitroprusside	IA

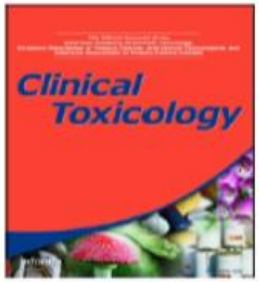
ANTİDOT TEDAVİLERİNDE YENİLİKLER

- Sistemik biyodetoksifikasyonda kullanılan geniş spektrumlu nanoantidotlar (nanotidotlar)
    1. İntralipid Emülsiyonu
    2. Lipozomlar
    3. Nanopartiküller
- Neuroglobin
- Hemodinamik anstabil veya standart tedaviye rezistan beta bloker ve Ca kanal blokerı toksisitelerinde yeni tedavi seçenekleri
- Yeni jenerasyon antikoagülan toksisitesi için geliştirilen antidotlar
- Antikorlar
- Nonimmün makromolekül bağlayıcılar
    1. Aptamer antikoagülanlara karşı geliştirilen antidotlar
    2. Sugammadex
- Organofosfat toksisitesinde yenilikler

İNTRALİPİD EMÜLSİYONU



İNTRALİPİD EMÜLSİYONU



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Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning

Sophie Gosselin, Lotte C. G. Hoegberg, Robert. S. Hoffman, Andis Graudins, Christine M. Stork, Simon H. L. Thomas, Samuel J. Stellpflug, Bryan D. Hayes, Michael Levine, Martin Morris, Andrea Nesbitt-Miller, Alexis F. Turgeon, Benoit Bailey, Diane P. Calello, Ryan Chuang, Theodore C. Bania, Bruno Mégarbane, Ashish Bhalla & Valéry Lavergne

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Table 3. Executive summary of indications regarding the use of ILE in poisoning.

Toxins	Clinical situations (strength of recommendation & level of evidence)[a]
Local anesthetics	
Bupivacaine	In cardiac arrest: we recommend using ILE (1D) In life-threatening toxicity: we suggest using ILE as part of treatment modalities (2D) and we recommend using ILE if other therapies fail/in last resort (1D) In non-life-threatening toxicity: neutral recommendation
All other local anesthetics	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D) In non-life-threatening: neutral recommendation
Non-local anesthetics	
Antidysrhythmics Class 1	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Amitriptyline	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE as part of treatment modalities (2D)
Other tricyclic antidepressants	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE in any circumstances (2D)
Baclofen	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Beta receptor antagonists (Lipid-soluble)	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Beta receptor antagonists (Non lipid-soluble)	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D)
Bupropion	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Calcium channel blockers: Diltiazem and verapamil	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Calcium channel blockers: Dihydropyridines	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE in any circumstances (2D)
Cocaine	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D)
Diphenhydramine	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE otherwise (2D)
Other antihistamines	Insufficient data
Ivermectin	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Other insecticides	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Lamotrigine	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D)
Malathion	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Other pesticides	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Olanzapine	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Other antipsychotics	In cardiac arrest: neutral recommendation In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)
Selective serotonin reuptake inhibitors	In cardiac arrest: neutral recommendation In life-threatening toxicity: neutral recommendation In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)

[a]Neutral position if not otherwise specified.

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AAEM Position Paper

USE OF INTRAVENOUS FAT EMULSION IN THE EMERGENCY DEPARTMENT FOR THE CRITICALLY ILL POISONED PATIENT

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☐ **Abstract—Background: Multiple case reports of using intravenous fat emulsion (IFE) as an antidote for human poisoning from various xenobiotics have been published over the last decade. Given the rapidly evolving field, emergency physicians may be uncertain about the indications, timing, and dose for IFE treatment. Methods: A PubMed literature search was conducted from January 1996 to November 2015 and limited to human studies written in English and articles with relevant keywords. Guideline statements and nonsystematic reviews were excluded. Studies identified then underwent a structured review of their results. Results: There were 986 papers fulfilling the search criteria screened, and 85 appropriate articles were rigorously reviewed in detail. Recommendations were given on indications, timing, and dose of IFE. Most of these were based on case reports and anecdotal experience. Discussion: In critically ill patients with refractory shock or cardiac arrest after a suspected overdose of local anesthetics or selected xenobiotics, IFE may be considered as a potentially beneficial adjunctive treatment. Despite an abundance of reports on the use of IFE on xenobiotics poisoning, the quality of evidence is suboptimal and fraught with reporting bias. Conclusions: IFE may be an effective antidote in poisonings from various xenobiotics. However, further research is needed to determine its optimal circumstances, timing, and dose of use.** © 2016 Elsevier Inc.

55 (68)	Geib AJ, Liebelt E, Manini AF;Toxicology Investigators' Consortium (ToxIC). Clinical experience with intravenous lipid emulsion for drug-induced cardiovascular collapse. J Med Toxicol 2012;8:10–4.	D	Good	Retrospective review (n = 9)
56 (69)	Haesendonck R, de Winter S, Verelst S, et al. Intravenous lipid emulsion for intentional Chloroquine poisoning. Clin Toxicol (Phila) 2012;50:223.	E	Poor	Case report (n = 1)
57 (22)	Levine M, Brooks DE, Franken A, et al. Delayed-onset seizure and cardiac arrest after amitriptyline overdose, treated with intravenous lipid emulsion therapy. Pediatrics 2012;130:e432–8.	E	Adequate	Case report (n = 1) Drug levels included prior to and after IFE given
58 (23)	McAllister RK, Tutt CD, Colvin CS. Lipid 20% emulsion ameliorates the symptoms of olanzapine toxicity in a 4-year-old. Am J Emerg Med 2012;30: 1012e1–2.	E	Poor	Case report (n = 1)
59 (70)	Taftachi F, Sanaei-Zadeh H, Sepehrian B, et al. Lipid emulsion improves Glasgow coma scale and decreases blood glucose level in the setting of acute non-local anesthetic drug poisoning—a randomized controlled trial. Eur Rev Med Pharmacol Sci 2012;16(Suppl	B	Good	Randomized controlled trial (n = 30)
68 (79)	Gil HW, Park JS, Park SH, et al. Effect of intravenous lipid emulsion in patients with acute glyphosate intoxication. Clin Toxicol (Phila) 2013;51:767–71.	D	Good	Case-control study (n = 44)
69 (80)	Moon HJ, Lee JW. Availability of intravenous lipid emulsion therapy on endosulfan-induced cardiovascular collapse. Am J Emerg Med 2013;31:886.e1–2.	E	Poor	Case report (n = 1)

(Ref. #)	Article Information	Grade	Quality	Design/Size
76 (87)	Sebe A, Dişel NR, Açıkalın Akpınar A, et al. Role of intravenous lipid emulsions in the management of calcium channel blocker and β-blocker overdose: 3 years experience of a university hospital. Postgrad Med 2015;127:119–24.	D	Adequate	Retrospective study (n = 15)
77 (88)	Calenda E, Dinescu SA. Failure of lipid emulsion to reverse neurotoxicity after an ultrasound-guided axillary block with ropivacaine and mepivacaine. J Anesth 2009;23:472–3.	E	Poor	Case report (n = 1)
78 (89)	Watt P, Malik D, Dyson L. Gift of the glob—is it foolproof? Anaesthesia 2009;64:1031–3.	E	Poor	Case series (n = 2)
79 (90)	West PL, McKeown NJ, Hendrickson RG. Iatrogenic lipid emulsion overdose in a case of amlodipine poisoning. Clin Toxicol (Phila) 2010;48: 293–6.	E	Adequate	Case report (n = 1) Drug levels included after IFE given
80 (91)	Kiberd MB, Minor SF. Lipid therapy for the treatment of a refractory amitriptyline overdose. CJEM 2012;14:193–7.	E	Poor	Case report (n = 1)
81 (92)	Kundu R, Almasri H, Moza A, et al. Intravenous lipid emulsion in wide complex arrhythmia with alternating bundle branch block pattern from cocaine overdose. Kardiol Pol 2013;71:1073–5.	E	Poor	Case report (n = 1)
82 (93)	Bazerbachi F, Rank K, Chan A. Intravenous lipid rescue and ropivacaine systemic toxicity. J Anesth 2014;28:139.	E	Poor	Case report (n = 1)
83 (94)	Downes MA, Calver LA, Isbister GK. Intralipid therapy does not improve level of consciousness in overdoses with sedating drugs: a case series. Emerg Med Australas 2014;26:286–90.	D	Adequate	Retrospective chart review (n = 9)
84 (95)	Rodríguez B, Wilhelm A, Kokko KE. Lipid emulsion use precluding renal replacement therapy. J Emerg Med 2014;47:635–7.	E	Poor	Case report (n = 1)
85 (96)	Fettiplace MR, Akpa BS, Rubinstein I, et al. Confusion about Infusion: rational volume limits for intravenous lipid emulsion during treatment of oral overdoses. Ann Emerg Med 2015;66:185–8.	F	Poor	Rational conjecture/Editorial

İNTRALİPİD EMÜLSİYONU (AHA 2015 Özel Durumlarda Resusitasyon)

5.2 2015 Recommendations—New and Updated

5.2.1 ACLS Modifications - Updated

It may be reasonable to administer ILE, concomitant with standard resuscitative care, to patients with local anesthetic systemic toxicity and particularly to patients who have premonitory neurotoxicity or cardiac arrest due to bupivacaine toxicity. (Class IIb, LOE C-EO)

It may be reasonable to administer ILE to patients with other forms of drug toxicity who are failing standard resuscitative measures. (Class IIb, LOE C-EO)

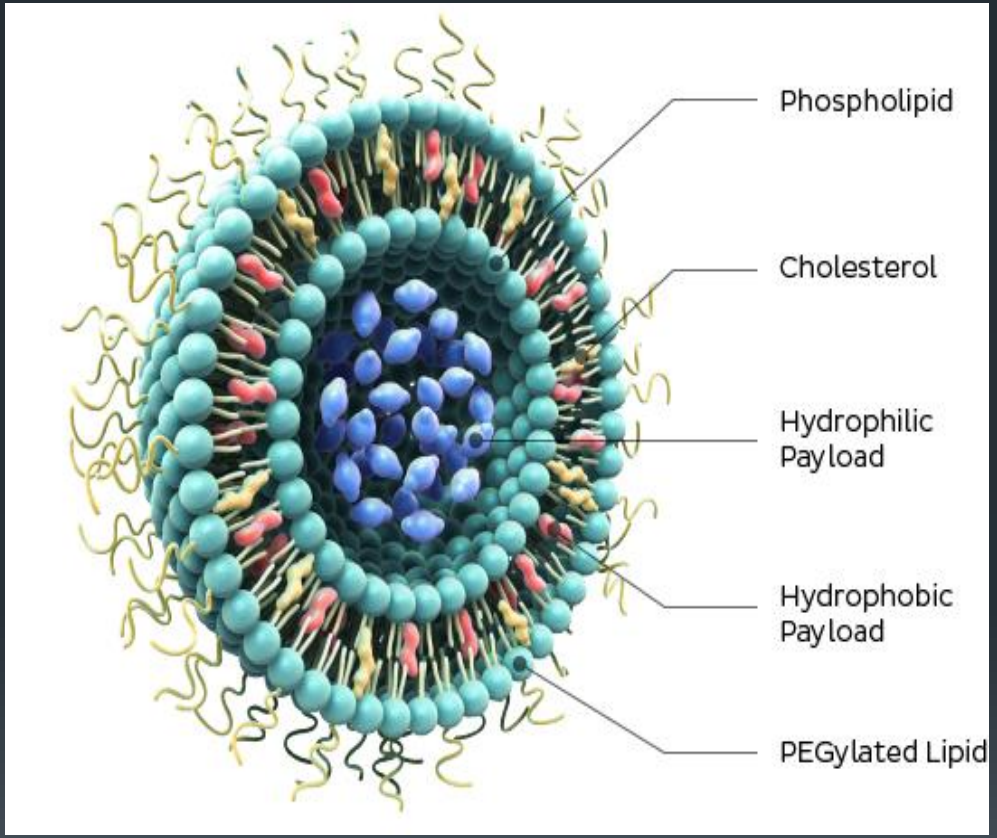
Önerilen doz: %20 lik emülsiyondan1.5 ml/kg 1 dakikada İV bolus (70 kg olan bir hasta için ortalama 100 ml), Asistol ve nabızsız elektriksel aktivitede aynı dozda bolus tekrar verilebilir.

takiben 0.25 ml/kg/dk hızda 60 dakika süre ile infüzyon (70 kg bir hasta için ortalama 18 ml/dk)

Dirençli hemodinamik anstabilite durumunda infüzyon hızı 2 katına çıkarılabilir. Hemodinamik stabilite sağlandıktan sonra en az 10 dk daha infüzyona devam edilmelidir.

LİPOZOMLAR

- Çift konsantrik fosfolipid tabaka tarafından çevrilmiş iki veya daha fazla sıvı çekirdek içeren içi boş sferik veziküllerdir.



LİPOZOMLAR

- İyonize ilaçları çok etkin bir şekilde yakalama ve taşıyabilme yeteneğine sahiptirler.
- Transmembran pH gradient multilameller lipozomların amitriptilin toksisitesine bağlı kardiyotoksik etkiyi geri çevirdiği tespit edilmiştir.
- Yüksek doz diltiazeme bağlı sistemik hipotansiyonu ortadan kaldırdıkları bulunmuştur.
- İLE'dan invitro ve invivo daha potenttir (İLE'dan 20 kat fazla toksini yakalar, iyileşme süresi %30 daha hızlı)

ACS Nano. 2010 Dec 28;4(12):7552-8. doi: 10.1021/nn101924a. Epub 2010 Nov 10.

ACS Publications

Transmembrane pH-gradient liposomes to treat cardiovascular drug intoxication.

Bertrand N[1], Bouvet C, Moreau P, Leroux JC.

Biomaterials. 2012 May;33(13):3578-85. doi: 10.1016/j.biomaterials.2012.01.042. Epub 2012 Feb 11.

ELSEVIER FULL-TEXT ARTICLE

Treatment of calcium channel blocker-induced cardiovascular toxicity with drug scavenging liposomes.

Forster V[1], Luciani P, Leroux JC.

NANOPARTİKÜLLER

Sci Transl Med. 2015 Jun 3;7(290):290ps14. doi: 10.1126/scitranslmed.3008736.

Nano-antidotes for drug overdose and poisoning.

Forster V[1], Leroux JC[2].

Author information

Abstract

The number of intoxications from xenobiotics--natural or synthetic foreign chemicals, or substances given in higher doses than typically present in humans--has risen tremendously in the last decade, placing poisoning as the leading external cause of death in the United States. This epidemic has fostered the development of antidotal nanomedicines, which we call "nano-antidotes," capable of efficiently neutralizing offending compounds in situ. Although prototype nano-antidotes have shown efficacy in proof-of-concept studies, the gap to clinical translation can only be filled if issues such as the clinical relevance of intoxication models and the safety profile of nano-antidotes are properly addressed. As the unmet medical needs in resuscitative care call for better treatments, this Perspective critically reviews the recent progress in antidotal medicine and emerging nanotechnologies.

The rational design of a synthetic polymer nanoparticle that neutralizes a toxic peptide in vivo

Yu Hoshino[a,1], Hiroyuki Koide[b], Keiichi Furuya[c], Walter W. Haberaecker III[b], Shih-Hui Lee[b], Takashi Kodama[d], Hiroaki Kanazawa[e], Naoto Oku[c], and Kenneth J. Shea[b,1]

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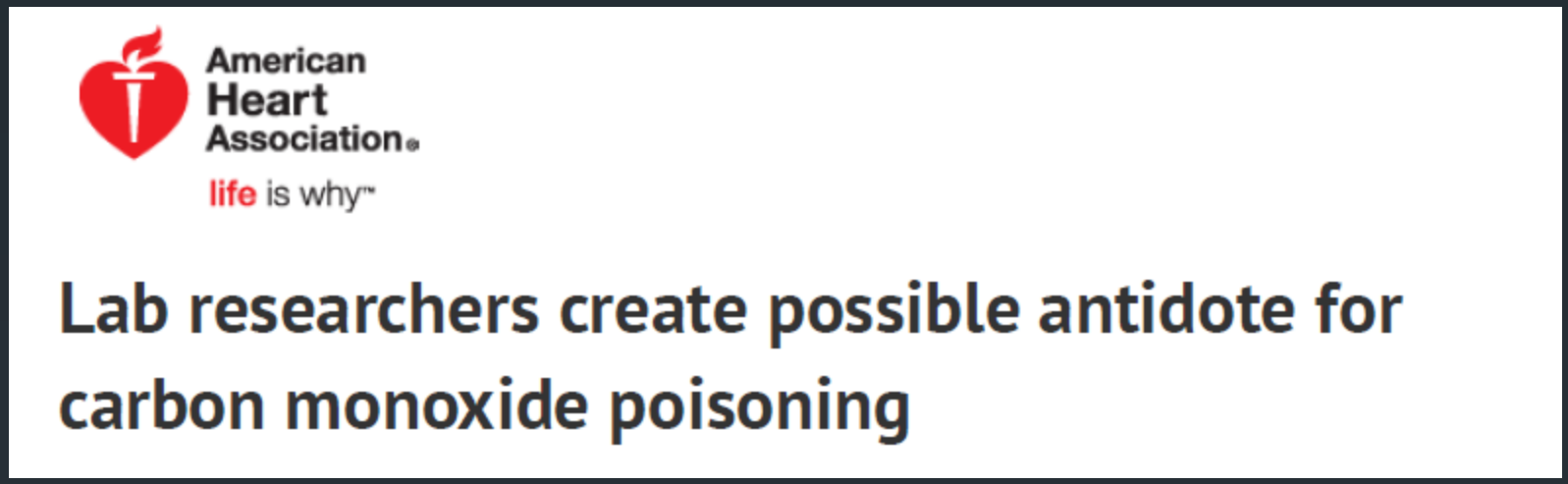
Edited* by Peter M. Rentzepis, University of California Irvine, Irvine, CA, and approved November 8, 2011 (received for review August 5, 2011)

Synthetic polymer nanoparticles (NPs) that bind venomous molecules and neutralize their function in vivo are of significant interest as "plastic antidotes." Recently, procedures to synthesize polymer NPs with affinity for target peptides have been reported. However, the performance of synthetic materials in vivo is a far greater challenge. Particle size, surface charge, and hydrophobicity affect not only the binding affinity and capacity to the target toxin but also the toxicity of NPs and the creation of a "corona" of proteins around NPs that can alter and or suppress the intended performance. Here, we report the design rationale of a plastic antidote for in vivo applications. Optimizing the choice and ratio of functional monomers incorporated in the NP maximized the binding affinity and capacity toward a target peptide. Biocompatibility tests of the NPs in vitro and in vivo revealed the importance of tuning surface charge and hydrophobicity to minimize NP toxicity and prevent aggregation induced by nonspecific interactions with plasma proteins. The toxin neutralization capacity of NPs in vivo showed a strong correlation with binding affinity and capacity in vitro. Furthermore, in vivo imaging experiments established the NPs accelerate clearance of the toxic peptide and eventually accumulate in macrophages in the liver. These results provide a platform to design plastic antidotes and reveal the potential and possible limitations of using synthetic polymer nanoparticles as plastic antidotes.

arginine-rich proteins (9). It has also been demonstrated that polymer NPs synthesized with an optimized combination of functional monomers can capture target molecules (10) and neutralize its function (6). However, little has been reported about a general design rationale for achieving NPs with molecular recognition for in vivo applications (3, 8).

For NPs to neutralize the function of target molecules in vivo, they must be stable, biologically inert, and nontoxic. They also have to remain in the bloodstream for a sufficient time to enable capture of target molecules. It has been reported that the NPs smaller than approximately 8 nm will be cleared rapidly from the blood stream by the renal system and NPs larger than 200 nm will be sequestered by the mononuclear phagocytic system (MRS) in the liver and spleen (11–14). Hydrophobicity, charge, flexibility, and shape of NPs are also important; for example hydrophobic particles induce formation of a corona of serum proteins around the surface and strongly charged NPs will be phagocytosed by MRS faster than neutral particles (11–18). Although the size of NPs can be adjusted, surface charges and hydrophobicity of plastic antidotes cannot always be optimized to increase circulation time since surface functionality must be designed to maximize affinity and capacity to target molecules. This limitation requires a fundamentally different rationale for designing nanoparticles for toxin neutralization or applications such as

NEUROGLOBİN



- **Vücutta oksijen taşıyan veya oksijene bağlanan proteinlerin ailesinden.**
- **2000 yılında keşfedilmiş, görevi o yıllarda tam anlaşılamamış.**
- **Mutant neuroglobin (H64Q neuroglobin) toksik gazları mıknatıs gibi çeker. CO'e Hemoglobinden 500 kat daha sıkı bağlanır.**

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Sci Transl Med. 2016 December 07; 8(368): 368ra173. doi:10.1126/scitranslmed.aah6571.

Five-coordinate H64Q neuroglobin as a ligand-trap antidote for carbon monoxide poisoning

Ivan Azarov[1,†], Ling Wang[1,2,†], Jason J. Rose[1,2,†], Qinzi Xu[1], Xueyin N. Huang[1], Andrea Belanger[5], Ying Wang[2], Lanping Guo[2], Chen Liu[5], Kamil B. Ucer[5], Charles F. McTiernan[1,2], Christopher P. O'Donnell[1,2], Sruti Shiva[1,3,4], Jesús Tejero[1,2], Daniel B. Kim-Shapiro[5,6], and Mark T. Gladwin[1,2,*]

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Abstract

Background: Carbon monoxide (CO) poisoning is a leading cause of poisoning deaths worldwide, with no available antidotal therapy. Neuroglobin (Ngb) is a six-coordinate hemoprotein, with the heme iron coordinated by two histidine residues. We mutated the distal histidine to glutamine (H64Q), combined with three surface thiol substitutions, forming a five-coordinate heme protein (Ngb-H64Q-CCC). This molecule exhibits an unusually high affinity for gaseous ligands, with a P50 value for oxygen of 0.05 mmHg. This finding informs our primary hypothesis that a mutant five-coordinated Ngb binds CO with very high affinity and can be developed as a novel specific antidotal therapy to bind, chelate and eliminate CO for the treatment of CO poisoning.

Methods and Results: We measured CO binding affinities from recombinant Ngb molecules and from hemoglobin (Hb) using laser flash photolysis. It was found Ngb-H64Q-CCC bound CO almost 500 times stronger than Hb. We evaluated CO transfer from carboxy-Hb (CO-Hb) to Ngb-H64Q-CCC under anaerobic and aerobic conditions. The half-lives of CO dissociation from free Hb and red blood cells in the presence of Ngb-H64Q-CCC were calculated via single exponential fits. Incubation of Ngb-H64Q-CCC with 100% CO-saturated cell–free or human red blood cell-encapsulated Hb reduced the half-life of carboxy-Hb (CO-Hb) to 0.11 and 0.41 minutes respectively, compared with 222 and 99 minutes in air. In a moderate CO poisoning mouse model, after 50 minutes of CO exposure blood CO-Hb levels plateaued at 64 ± 1%, which dropped at the first 5min after CO stopped by an average of 35.0 ± 2.1% in Ngb-H64Q-CCC treated group versus 13.3 ± 0.6% in PBS group and 27.4 ± 1.6% in the group that received 100% oxygen inhalation ($P < 0.05$), followed by rapid renal elimination of CO-bound Ngb-H64Q-CCC. Moreover, Ngb-H64Q-CCC infusion in a lethal CO poisoning mouse model significantly lowered mortality rate (20% in Ngb-H64Q-CCC vs. 100% in PBS group) and recovered heart rate and blood pressure.

Conclusion: The current studies identify a novel specific antidotal therapy for CO poisoning that rapidly scavenge CO from RBCs and tissues within minutes, and improve survival as well, providing for a potential paradigm changing approach to the most common human poisoning.

BETA BLOKER- Ca KANAL BLOKER TOKSİSİTESİNDE YENİLİKLER

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12763

Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies

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[Correction added after initial online publication on 30 October 2015: the title has been revised.]

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Keywords
antidote, beta-receptor antagonist, calcium channel antagonist, overdose, poisoning

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Summary of common pharmacological agents used in the treatment of shock from calcium channel antagonist (CCB) and beta-adrenergic receptor antagonist (BB) poisoning

Indication	Treatment	Dosing	Desired clinical effect	Adverse events
Suspected or documented cardiogenic shock in BB or CCB intoxication	High-dose insulin euglycaemia	Loading dose 1 IU kg^{-1} Infusion 1–10 IU kg^{-1} h^{-1} With 50% glucose infusion to maintain euglycaemia	Positive inotrope Increased cardiac output Increased BP Reduced catecholamine infusion requirements	Hypoglycaemia Hypokalaemia Mild vasodilation No effect on heart rate
	Inotropic/chronotropic catecholamines:	Titrated infusion to effect	Adrenaline: Positive inotrope and chronotrope	Adrenaline: Possible increase in BP from alpha-adrenergic vasoconstriction with no increase or fall in cardiac output
	adrenaline	0.05–1 µg kg^{-1} min^{-1}	Increased contractility and heart rate → increased cardiac output and BP	Hyperglycaemia Lactic acidaemia Limb ischaemia
	Isoprenaline	0.5–5 µg min^{-1} (up to 20 µg min^{-1})	Isoprenaline: Positive inotrope and chronotrope Increased heart rate, contractility → increased cardiac output and BP	Isoprenaline: Ventricular arrhythmias Worsening of hypotension from beta-2 adrenoceptor stimulation
	Phosphodiesterase inhibitors (e.g. milrinone, enoximone)	Varies depending upon agent selected	Increased cardiac output	Vasodilation worsening hypotension Ventricular arrhythmias
CCB toxicity with suspected hypotension from cardiogenic shock and/or vasodilatory shock	Calcium infusion	Loading dose: 0.6 ml kg^{-1} of 10% calcium gluconate) Infusion: 0.6–1.6 ml kg^{-1} h^{-1} Aim for serum ionized calcium up to 2 × reference range	Increased BP from improved cardiac output and/or SVR	Effect can be transient No effect on heart rate
Suspected or documented vasodilatory shock from CCB poisoning	Alpha-adrenergic agonists (noradrenaline, phenylephrine, metaraminol)	Titrated infusion dosing to effect	Improvement in BP Increased SVR	Possible increase in BP from alpha-adrenergic vasoconstriction with no increase in cardiac output Hyperglycaemia Lactic acidaemia
	Vasopressin	Titrated dosing up to maximum of 0.04 IU min^{-1}	Improvement in BP Increased SVR	Limb ischaemia

BP, blood pressure; SVR, systemic vascular resistance.

Summary of treatments to consider in cases where shock or bradycardia is unresponsive to standard therapies

Treatment	Indication	Dosing	Desired effect	Potential adverse reactions
Glucagon	BB toxicity	Loading-dose:	Primarily positive chronotropic action	Nausea, vomiting
	Bradycardia and cardiogenic shock	5–10 mg Infusion: 2–5 mg h^{-1}	Increased heart rate →	Hyperglycaemia
			Increased BP	Not enough glucagon available to sustain infusion
Levosimendan	Cardiogenic shock	Variable	Increased cardiac output	Vasodilation worsening hypotension
				Ventricular arrhythmias
Cardiac transvenous/cutaneous pacing	Symptomatic bradycardia and heart block in BB and CCB poisoning	Not applicable	Increased heart rate	Failure to capture heart rate
				Heart rate may increase without change in BP
				Ventricular arrhythmia
				Ventricular perforation
Extracorporeal cardiac assist devices	Cardiogenic shock	Not applicable	Mechanical support of cardiac output	Local:
			Not effective in vasodilatory shock	Limb ischaemia, DVT
				Systemic:
				Coagulopathy, bleeding, haemolysis, septicaemia, systemic thromboembolism
Intravenous lipid emulsion	Refractory cardiogenic or vasodilatory shock	Loading dose: 1.5 ml kg^{-1} 20% lipid emulsion Infusion: 0.25 ml kg^{-1} min^{-1} to a total volume of 10 ml kg^{-1}	Improvement in BP, perfusion, heart rate	Lipaemic plasma. Inability to analyse blood biochemistry
				Blood hyperviscosity
				Pancreatitis
				Noncardiogenic pulmonary oedema
Methylene blue	Refractory vasodilatory shock	Loading dose 1–2 mg kg^{-1}	Improvement in hypotension	Blue discolouration of the skin, secretions
			Reduction in vasopressor dosing	Haemolysis
				Methaemoglobinaemia
				Serotonin syndrome in presence of serotonergic agonists, MAOIs, SSRIs

BB, beta-adrenergic receptor antagonist; BP, blood pressure; CCB, calcium channel antagonist; DVT, deep-vein thrombosis; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

YENİ JENERASYON ANTİKOAGÜLAN TOKSİSİTESİ

Curr Treat Options Neurol (2016) 18: 47
DOI 10.1007/s11940-016-0430-5

Critical Care Neurology (K Sheth, Section Editor)

New Oral Anticoagulants and Their Reversal Agents

Andrea Morotti, MD[1,*]
Joshua N. Goldstein, MD, PhD[1,2]

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Table 2. Specific DOAC antidotes

	Idarucizumab	Andexanet	Aripazine
Target	Dabigatran	Apixaban, Rivaroxaban, Edoxaban, LMWH, Fondaparinux	Dabigatran, Apixaban, Rivaroxaban, Edoxaban, LMWH, UFH, Fondaparinux
Structure	Humanized monoclonal antibody	Inactive truncated factor Xa	Synthetic molecule
Mechanism of action	Neutralization of free and clot-bound dabigatran	High affinity factor Xa inhibitor binding	Target binding through charge-charge interactions and hydrogen bonding
Dose	5 mg IV	210–420 mg IV bolus plus 2 h infusion at 4–8 mg/min	100–400 mg IV
Side effects	Skin reaction and hematoma at infusion site Epistaxis	Urticaria Flushing Dysgeusia Headache	Flushing Dysgeusia Headache

LMWH low molecular weight heparin, *UFH* unfractioned heparin, *IV* intravenous

ANTİKORLAR

- Digibind® (1986)
- DigiFab® (2001 FDA tarafından onaylandı)
- TriTab®
- Nikotin ve morfine karşı aşılar
- F(ab')2 fragmanları (kokain toksisitesinde)

Am J Ther. 2016 Nov/Dec;23(6):e1597-e1601.

Digoxin-Specific Antibody Fragment Dosing: A Case Series.

Chhabra N[1], Valento M, Bryant SM, Aks SE.

Author information

Abstract

Digoxin-specific antibody fragments (DSFab) are used for the treatment of poisoning by cardiac glycosides, such as pharmaceutical digoxin. Dosing of this therapy for chronic and acute poisonings is based on the steady-state serum concentrations of digoxin, historical data in acute ingestions, or empiric regimens purportedly based on the average requirements. Empiric dosing for adult patients involves utilization of 3-6 vials for chronic poisoning and 10-20 vials for acute poisoning. The aim of this study was to describe the average dosing requirements based on the steady-state serum concentration of digoxin or historical data and compare this with the empiric dosing regimens. We performed a retrospective analysis of cases over an 11-year period presented to the Illinois Poison Center where administration of DSFab was recommended. We identified 140 cases of chronic digoxin poisoning and 26 cases or acute digoxin poisoning for analysis. The average dose of DSFab recommended in the cases of chronic digoxin poisoning was 3.05 vials (SD ± 1.31). The average dose of DSFab recommended in the cases of acute digoxin poisoning was 6.33 vials (SD ± 5.26). These values suggest that empiric dosing regimens may overestimate the need for DSFab in cases of both chronic and acute poisonings of pharmaceutical digoxin.

Clin Toxicol (Phila). 2014 Sep-Oct;52(8):824-36. doi: 10.3109/15563650.2014.943907. Epub 2014 A

View full text

Digoxin-specific antibody fragments in the treatment of digoxin toxicity.

Chan BS[1], Buckley NA.

CONCLUSIONS: Digoxin-Fab is safe and indicated in all patients with life-threatening arrhythmias and an elevated digoxin concentration. However, calculated full neutralising doses of digoxin-Fab are expensive and may not be required. In acute poisoning, a small bolus of 80 mg, repeat if necessary, titrated against clinical effect, is likely to achieve equivalent benefits with much lower total doses. With chronic poisoning, it may be simplest to give 40 mg (1 vial) digoxin-Fab at a time and repeat after 60 min if there is no response.

Clin Toxicol (Phila). 2016 Jul;54(6):488-94. doi: 10.1080/15563650.2016.1175620. Epub 2016 Apr 2

View full text

Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1).

Chan BS[1,2], Isbister GK[2,3,4], O'Leary M[3,4], Chiew A[1,2], Buckley NA[2,5].

Author information

Abstract

CONTEXT: We hypothesized that in chronic digoxin toxicity, anti-digoxin antibodies (Fab) would be efficacious in binding digoxin, but this may not translate into improved clinical outcomes.

OBJECTIVE: This study aims to investigate changes in free digoxin concentrations and clinical effects on heart rate and potassium concentrations in chronic digoxin poisoning when anti-digoxin Fab are given.

MATERIALS AND METHODS: This is a prospective observational study. Patients were recruited if they have been treated with anti-digoxin Fab for chronic digoxin poisoning. Data was entered into a standardised prospective form, supplemented with medical records. Their serum or plasma was collected, analysed for free and bound digoxin and free anti-digoxin Fab concentrations.

RESULTS: From September 2013 to February 2015, 36 patients (median age, 78 years; 22 females) were recruited from 18 hospitals. Median heart rate (HR) was 49 beats/min. Initial median digoxin and potassium concentrations were 4.7 nmol/L (3.6 µg/L) (range: 2.3-11.2 nmol/L) and 5.3 mmol/L (range: 2.9-9.2 mmol/L) respectively. Beta-blockers (n = 18), calcium antagonists (n = 6), spironolactone and/or angiotensin blocking agents (n = 24) were also used concomitantly. Renal impairment and gastrointestinal symptoms were present in 31 (86%) and 22 (63%) patients respectively. Five patients died from conditions unrelated to digoxin toxicity. Median change in HR was 8 beats/min post-Fab with no effect on blood pressure; they were 4, 10 and 17 beats/min for the 1, 2 and ≥3 vials of anti-digoxin Fab groups respectively. Concomitant treatments with potassium lowering agents (12/36) and inotropic drugs (7/36) were used. Gastrointestinal effects resolved in all 22 patients. The median decrease for potassium was 0.3 mmol/L. Digoxin concentration reduced from 3.8 to 0 nmol/L post-Fab. There was a rebound observed in the free digoxin concentration in 25 patients but none had associated clinical deterioration.

CONCLUSIONS: One to two vials of anti-digoxin Fab initially bound all free digoxin confirming Fab efficacy. However, this was associated with only a moderate improvement in HR and potassium, suggesting bradyarrhythmia and hyperkalaemia may be from other co-morbidities.

KEYWORDS: Digoxin-Fab; digoxin intoxication; overdose

Biomaterials. 2017 Apr;123:107-117. doi: 10.1016/j.biomaterials.2017.01.038. Epub 2017 Jan 27.

ELSEVIER FULL-TEXT ARTICLE

Engineering of a hybrid nanoparticle-based nicotine nanovaccine as a next-generation immunotherapeutic strategy against nicotine addiction: A focus on hapten density.

Zhao Z[1], Powers K[2], Hu Y[1], Raleigh M[3], Pentel P[3], Zhang C[4].

Author information

Abstract

Although **vaccination** is a promising way to combat **nicotine** addiction, most traditional hapten-protein conjugate **nicotine** vaccines only show limited efficacy due to their poor recognition and uptake by immune cells. This study aimed to develop a hybrid nanoparticle-based **nicotine** vaccine with improved efficacy. The focus was to study the impact of hapten density on the immunological efficacy of the proposed hybrid nanovaccine. It was shown that the nanovaccine nanoparticles were taken up by the dendritic cells more efficiently than the conjugate vaccine, regardless of the hapten density on the nanoparticles. At a similar hapten density, the nanovaccine induced a significantly stronger immune response against **nicotine** than the conjugate vaccine in mice. Moreover, the high- and medium-density nanovaccines resulted in significantly higher anti-**nicotine** antibody titers than their low-density counterpart. Specifically, the high-density nanovaccine exhibited better immunogenic efficacy, resulting in higher anti-**nicotine** antibody titers and lower anti-carrier protein antibody titers than the medium- and low-density versions. The high-density nanovaccine also had the best ability to retain **nicotine** in serum and to block **nicotine** from entering the brain. These results suggest that the hybrid nanoparticle-based **nicotine** vaccine can elicit strong immunogenicity by modulating the hapten density, thereby providing a promising next-generation immunotherapeutic strategy against **nicotine** addiction.

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Bioorg Med Chem Lett. 2016 October 15; 26(20): 5078–5081. doi:10.1016/j.bmcl.2016.08.081.

Studies Towards the Improvement of an Anti-Cocaine Monoclonal Antibody for Treatment of Acute Overdose

Bin Zhou[a,b], **Lisa M Eubanks**[a,b], **Nicholas T Jacob**[a], **Beverly Ellis**[a,b], **Amanda J Roberts**[c], and **Kim D Janda**[a,b,d,*]

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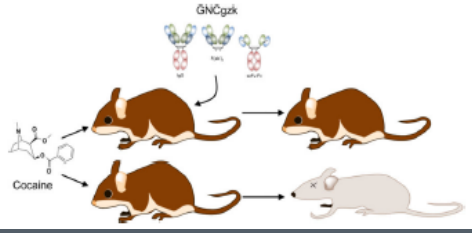
Abstract

There is currently no clinically-approved antidote for cocaine overdose. Efforts to develop a therapy via passive immunization have resulted in a human monoclonal antibody, GNCgzk, with a high affinity for cocaine (K_d = 0.18 nM). Efforts to improve the production of antibody manifolds based on this antibody are disclosed. The engineering of an HRV 3C protease cleavage site into the GNCgzk IgG has allowed for increased production of a $F(ab')_2$ with a 20% superior capacity to reduce mortality for cocaine overdose in mice.

Graphical abstract



- Antikokain monoklonal antikorlar kokain overdozu gerçekleştirilen ratlarda mortaliteyi %20 azaltıyor.

NON-İMMÜN MAKROMOLEKÜLER BAĞLAYICILAR

- Endojen veya egzojen substratlara yüksek affinitesi olan sentetik veya yarı sentetik polimerler.
- Sugammadex: Nöromusküler blokerların etkisini geri çevirir. Siklik oligosakkarit yapıda siklodekstrin.
- Aptamer antikoagülanlar için geliştirilmiş antidot

  Pegnivacogin – Anivamersen

J Clin Anesth. 2017 Sep;41:84-91. doi: 10.1016/j.jclinane.2017.06.006. Epub 2017 Jul 15.

ELSEVIER FULL-TEXT ARTICLE

Sugammadex efficacy for reversal of rocuronium- and vecuronium-induced neuromuscular blockade: A pooled analysis of 26 studies.

Herring WJ[1], Woo T[2], Assaid CA[2], Lupinacci RJ[2], Lemmens HJ[3], Blobner M[4], Khuenl-Brady KS[5].

Author information

Abstract

STUDY OBJECTIVE: To summarize and compare efficacy of **sugammadex** with neostigmine or placebo for **reversal** of rocuronium- or vecuronium-induced neuromuscular blockade (NMB), and to demonstrate consistency of **sugammadex** results across various patient populations.

DESIGN: Pooled analysis on data from 26 multicenter, randomized, Phase II and III studies.

SETTING: Operating room.

PATIENTS: 1855 adults undergoing surgery under general anesthesia and receiving rocuronium or vecuronium for NMB.

INTERVENTIONS: **Sugammadex** (2.0mg/kg at second twitch reappearance [T_2; moderate NMB], 4.0mg/kg at 1-2 post-tetanic counts [PTC; deep NMB] or 16.0mg/kg at 3min after rocuronium 1.2mg/kg), neostigmine or placebo.

MEASUREMENTS: Time to recovery of the train-of-four (TOF) ratio to 0.9.

MAIN RESULTS: Geometric mean (95% CI) times to recovery to TOF ratio of 0.9 were 1.9 (1.8-2.0) min following **sugammadex** 2.0mg/kg and 10.6 (9.8-11.6) min following neostigmine administration at T_2 after rocuronium, and 2.9 (2.5-3.4) min and 17.4 (13.4-22.6) min, respectively, after vecuronium. Recovery times were 2.2 (2.1-2.3) min following **sugammadex** 4.0mg/kg and 19.0 (14.8-24.6) min following neostigmine administered at a target of 1-2 PTC after rocuronium, and 3.8 (3.0-5.0) min and 67.6 (56.3-81.2) min after vecuronium. **Sugammadex** administered 3min after rocuronium 1.2mg/kg resulted in rapid recovery (1.7 [1.5-2.0] min). Modest increases in mean recovery time were associated with vecuronium use (+1.6min [78%; (61%-98%)] versus rocuronium), mild-to-moderate renal impairment (+0.4min [20%; (9%-32%)] versus normal renal function) and geographic location (+1.0min [38%; (25%-52%)] in subjects in USA/Canada versus Europe/Japan).

CONCLUSIONS: **Sugammadex** administered at recommended doses provides rapid and predictable **reversal** of rocuronium and vecuronium-induced moderate and deep NMB, and effective **reversal** 3min after rocuronium 1.2mg/kg. Robust recovery was seen across various patient factors, providing further confirmation of labeled dose recommendations.

MEDICAL SCIENCE MONITOR

ANIMAL STUDY

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Comparison of Effects of Separate and Combined Sugammadex and Lipid Emulsion Administration on Hemodynamic Parameters and Survival in a Rat Model of Verapamil Toxicity

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Toxicity of calcium channel blockers leads to high patient mortality and there is no effective antidote. The benefit of using 20% lipid emulsion and sugammadex has been reported. The present study measured the effect of sugammadex and 20% lipid emulsion on hemodynamics and survival in a rat model of verapamil toxicity.

Material/Methods: In this single-blinded randomized control study, rats were separated into 4 groups of 7 rats each: Sugammadex (S), Sugammadex plus 20% lipid emulsion (SL), 20% lipid emulsion (L), and control (C). Heart rates and mean arterial pressures were monitored and noted each minute until death.

Results: Average time to death was 21.0±9.57 minutes for group C, 35.57±10.61 minutes for group S, 37.14±16.6 minutes for group L and 49.86±27.56 minutes for group SL. Time to death was significantly longer in other groups than in the control group ($p<0.05$).

Conclusions: Verapamil overdose is has a comparatively high mortality rate and there is no effective antidote. Treatment generally involves gastric decontamination and symptomatic treatment to counteract the drug's negative effects. In animal studies sugammadex and lipid emulsion had a positive effect on survival in patients with calcium channel blocker toxicity. Sugammadex and intralipid increased survival in a rat model of verapamil toxicity. The combination of both drugs may decrease cardiotoxicity. Sugammadex alone or combined with 20% lipid emulsion reduce the need for inotropic agents. The mechanism requires clarification with larger studies.

T.C.

SELÇUK ÜNİVERSİTESİ

TIP FAKÜLTESİ

“Trisiklik Antidepresan İntoksikasyonunda Sugammadexin Etkisi”

Dr.Hamide ALP

TIPTA UZMANLIK TEZİ

ACİL TIP ANABİLİM DALI

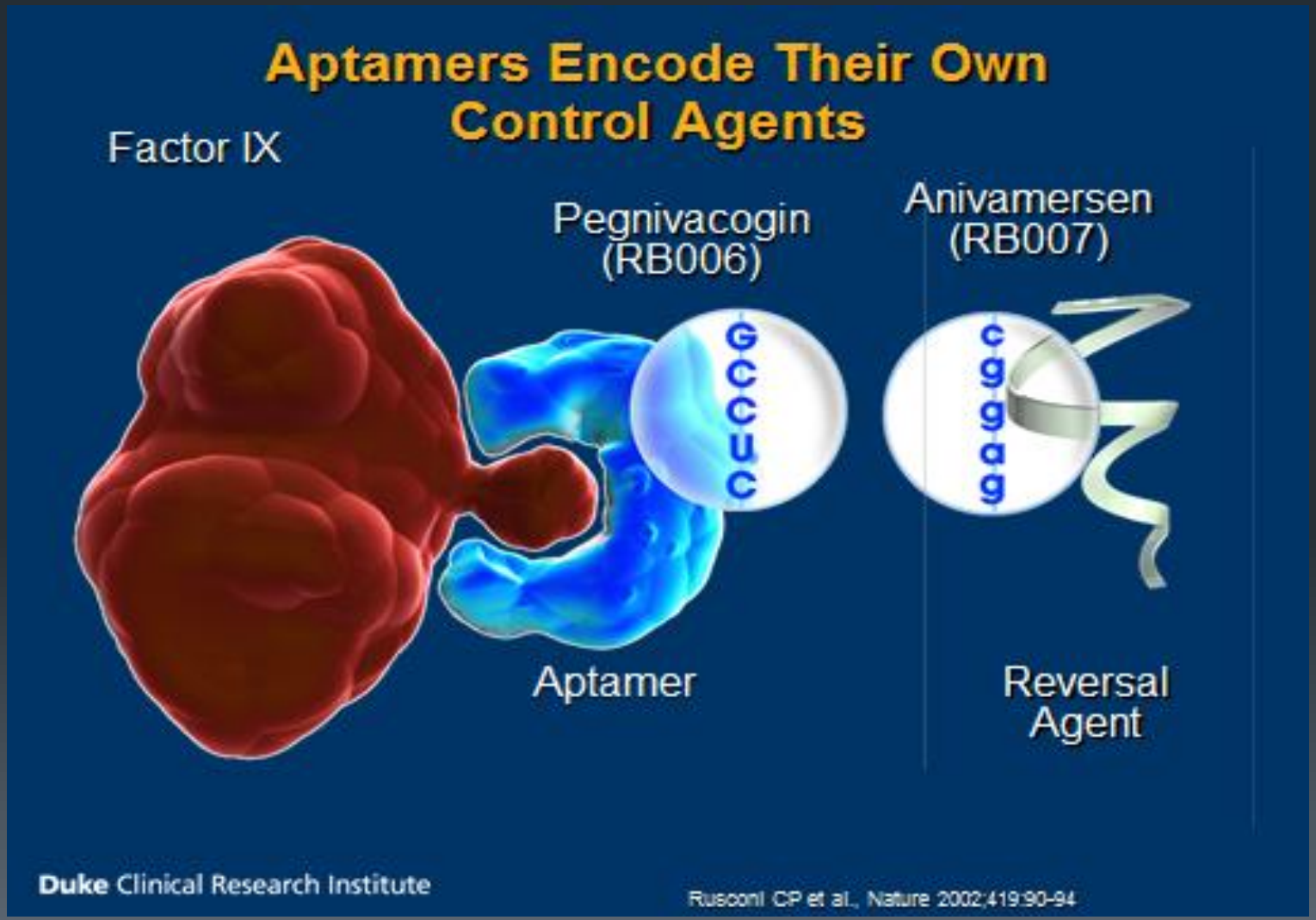
Danışman

“Prof. Dr. Ayşegül BAYIR”

Apoptotik Indeks	Beyin Frontal Lob	Kalp Endokard
Kontrol	%6	%6,8
İntoksikasyon	%36,3	%28
Bikarbonat	%24,9	%20,3
Sugammadex	%14,6	%13,2

Yaşam Süresi	Survi (Dakika)
Kontrol	120,0±0,00
İntoksikasyon	101,3±37,20
Bikarbonat	92,50±37,98
Sugammadex	120,0±0,00

APTAMER ANTİKOAGÜLAN ANTİDOTLARI



ORGANOFOSFAT TOKSİSİTESİ TEDAVİSİNDE YENİLİKLER

British Journal of Clinical Pharmacology

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Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new

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Keywords
insecticide, organophosphorus, poisoning

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Pharmacological treatments available for organophosphorus (OP) poisoning

Drug name	Type	Dose	Reference
Atropine	Anti-muscarinic	•Give a bolus loading dose of 0.6 to 3 mg, rapidly IV •Then administer doubling doses every 5 min until the patient is atropinized (HR >80 bpm, SBP > 80 mmHg, clear lungs) •Once the patient is atropinized, give an infusion of 10–20% of the total dose required to atropinize the patient each hour in 0.9% saline chloride •Watch the patient carefully for recurrent cholinergic toxicity or onset of atropine toxicity (see below) •If cholinergic toxicity recurs at any point, restart the bolus doses until the patient is atropinized again and increase the infusion rate by 20% per hour •If the patient becomes atropine toxic (tachycardia, absent bowel sounds, hyperthermia, delirium, urinary retention), stop the infusion for 30 min and then start again at a 20% lower dose	[8, 25]
Pralidoxime	Oxime AChE reactivator	•Give a loading dose of 20–30 mg kg^{-1} over 30 min •This dose can be repeated at 6–8 h intervals •Alternatively, a continuous infusion of 5–10 mg kg^{-1} h^{-1} can be given in 0.9% sodium chloride •The duration of treatment is uncertain. Treatment can be stopped at 48 h and then restarted if clinical or electrophysiological deterioration occurs. Monitoring of red cell AChE activity can be helpful	[26, 28]
Obidoxime	Oxime AChE reactivator	•Give a loading dose of 250 mg over 30 min •Then give a continuous infusion of 750 mg every 24 h until clinical recovery	[26, 28]
Diazepam	GABA-A agonist	Give 10–20 mg IV to agitated patients or patients with impaired respiration for whom intubation and ventilation are available	[42]

Doses are given for the antidotes widely used for OP insecticide poisoning. The evidence for these doses is generally weak (see text). AChE, acetylcholinesterase; bpm, beats per minute; GABA, gamma-aminobutyric acid; HR, heart rate; IV, intravenously; SBP, systolic blood pressure.

ORGANOFOSFAT TOKSİSİTESİ TEDAVİSİNDE YENİLİKLER

- Magnezyum Sülfat
- Antimuskarinikler
- Cyclodextrinler
- Sodyum bikarbonat
- Klonidin
- Nikotinik Reseptör Antagonistleri
- Beta Agonistler
- Lipid Emülsiyonu
- OP Hidrolaz
- Yeni Oksimler

Biol Trace Elem Res. 2010 Feb;133(2):227-35. doi: 10.1007/s12011-009-8418-6. Epub 2009 Jun 6.

SpringerLink FULL-TEXT ARTICLE

Cardiac effects of magnesium sulfate pretreatment on acute dichlorvos-induced organophosphate poisoning: an experimental study in rats.

Gunay N[1], Kekec Z, Demiryurek S, Kose A, Namiduru ES, Gunay NE, Sari I, Demiryurek AT.

Author information

Abstract

Although atropine and oximes are traditionally used in the management of **organophosphate poisoning**, investigations have been directed to finding additional therapeutic approaches. Thus, the aim of this study was to evaluate the cardiac effects of **magnesium sulfate** pretreatment on dichlorvos intoxication in rats. Rats were randomly divided into three groups as control, dichlorvos, and **magnesium sulfate** groups. After 6 h of dichlorvos or corn oil (as a vehicle) injection, venous blood samples were collected, and cardiac tissue samples were obtained. Biochemical analyses were performed to measure some parameters on serum and cardiac tissue. Immunohistochemical analyses of apoptosis and inducible nitric oxide (NO) synthase showed no change in cardiac tissue. Serum cholinesterase levels were markedly depressed with dichlorvos, and further suppressed markedly with **magnesium sulfate** pretreatment. Although we have demonstrated that serum NO levels in dichlorvos and **magnesium sulfate** groups were lower than the control group, cardiac tissue NO levels in **magnesium sulfate** group were higher than the other two groups. Mortality was not significantly affected with **magnesium sulfate** pretreatment. Uncertainty still persists on the right strategies for the treatment of **organophosphate** acute **poisoning**; however, it was concluded that our results do not suggest that **magnesium sulfate** therapy is beneficial in the management of acute dichlorvos-induced **organophosphate poisoning**, and also further studies are required.

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ORGAN TOXICITY AND MECHANISMS

Magnesium sulfate treatment against sarin poisoning: dissociation between overt convulsions and recorded cortical seizure activity

Shahaf Katalan · Shlomi Lazar · Rachel Brandeis · Ishai Rabinovitz · Inbal Egoz · Ettie Grauer · Eugenia Bloch-Shilderman · Lily Raveh

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Abstract Sarin, a potent organophosphate cholinesterase inhibitor, induces an array of toxic effects including convulsions. Many antidotal treatments contain anticonvulsants to block seizure activity and the ensuing brain damage. Magnesium sulfate (MGS) is used to suppress eclamptic seizures in pregnant women with hypertension and was shown to block kainate-induced convulsions. Magnesium sulfate was evaluated herein as an anticonvulsant against sarin poisoning and its efficacy was compared with the potent anticonvulsants midazolam (MDZ) and caramiphen (CRM). Rats were exposed to a convulsant dose of sarin (96 μg/kg, im) and 1 min later treated with the oxime TMB4 and atropine to increase survival. Five minutes after initiation of convulsions, MGS, CRM, or MDZ were administered. Attenuation of tonic–clonic convulsions was observed following all these treatments. However, radio-telemetric electro-corticography (ECoG) monitoring demonstrated sustained seizure activity in MGS-injected animals while this activity was completely blocked by MDZ and CRM. This disrupted brain activity was associated with marked increase in brain translocator protein levels, a marker for brain damage, measured 1 week following exposure. Additionally, histopathological analyses of MGS-treated group showed typical sarin-induced brain injury excluding the hippocampus that was partially protected. Our results clearly show that MGS demonstrated misleading features as an anticonvulsant against sarin-induced seizures. This stems from the dissociation observed between overt convulsions and seizure activity. Thus, the presence or absence of motor convulsions may be an unreliable indicator in the assessment of clinical status and in directing adequate antidotal treatments following exposure to nerve agents in battle field or terror attacks.

Keywords Sarin · Magnesium sulfate · Midazolam · Caramiphen · TSPO · ECoG

Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
CNS	Central nervous system
CRM	Caramiphen
ECoG	Electrocorticogram
GFAP	Glial fibrillary acidic protein
Glu	Glutamate
MDZ	Midazolam
MGS	Magnesium sulfate
MAP-2	Microtubule-associated protein 2
NeuN	Neuronal nuclear antigen
NMDA	N-Methyl-D-Aspartate
OP	Organophosphorous
TA	TMB4 + Atropine
TSPO	Translocator protein

Introduction

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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.

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Review

Caramiphen edisylate: An optimal antidote against organophosphate poisoning

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ABSTRACT

Potent cholinesterase inhibitors such as sarin, induce an array of harmful effects including hypersecretion, convulsions and ultimately death. Surviving subjects demonstrate damage in specific brain regions that lead to cognitive and neurological dysfunctions. An early accumulation of acetylcholine in the synaptic clefts was suggested as the trigger of a sequence of neurochemical events such as an excessive outpour of glutamate and activation of its receptors. Indeed, alterations in NMDA and AMPA central receptors' densities were detected in brains of poisoned animals. Attempts to improve the current cholinergic-based treatment by adding potent anticonvulsants or antiglutamatergic drugs produced unsatisfactory results. In light of recent events in Syria and the probability of various scenarios of military or terrorist attacks involving organophosphate (OP) nerve agent, research should focus on finding markedly improved countermeasures. Caramiphen, an antimuscarinic drug with antiglutamatergic and GABAergic facilitating properties, was evaluated in a wide range of animals and experimental protocols against OP poisoning. Its remarkable efficacy against OP exposure was established both in prophylactic and post-exposure therapies in both small and large animals. The present review will highlight the outstanding neuroprotective effect of caramiphen as the optimal candidate for the treatment of OP-exposed subjects.

NeuroToxicology 55 (2016) 33–39

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NeuroToxicology

Full length article

Therapeutic and reactivating efficacy of oximes K027 and K203 against a direct acetylcholinesterase inhibitor

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Dichlorvos
Rats
Acethylcholinesterase
Efficacy

ABSTRACT

As oxime-based structures are the only causal antidotes to organophosphate (OP)-inhibited acetylcholinesterase (AChE), the majority of studies on these have been directed towards their synthesis and testing. In this study, experimental bispyridinium oximes K027 and K203, which have shown promising results in the last decade of research, were examined *in vivo* for their therapeutic and reactivating ability in acute poisoning by the direct AChE-inhibitor dichlorvos (DDVP), used as a dimethyl OP structural model. Additionally, the efficacy of oximes K027 and K203 was compared with the efficacy of four oximes (pralidoxime, trimedoxime, obidoxime and HI-6), already used in efficacy experiments and human medicine. To evaluate therapeutic efficacy, groups of Wistar rats were treated with equitoxic doses of oximes (5% LD_{50}, i.m.) and/or atropine (10 mg/kg, i.m.) immediately after s.c. DDVP challenge (4–6 doses). Using the same antidotal protocol, AChE activity was measured in erythrocytes, diaphragm and brain 60 min after s.c. DDVP exposure (75% LD_{50}). The oxime K027 was the most efficacious in reducing the DDVP induced lethal effect in rats, while the oxime K203 was more efficacious than trimedoxime, pralidoxime and HI-6. Significant reactivation of DDVP inhibited AChE was achieved only with oxime K027 or its combination with atropine in erythocytes and the diaphragm. Moreover, the acute i.m. toxicity of oxime K027 in rats was lower than all other tested oximes. The results of this study support previous studies considering the oxime K027 as a promising experimental oxime structure for further testing against structurally-different OP compounds.

Original Paper

HET

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The effects of ubiquinone (CoQ10) on heart tissue in cardiac toxicity related to organophosphate poisoning

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Abstract

The aim of this study was to examine the effects of ubiquinone (CoQ10) on heart tissue and erythrocytes in acute organophosphate poisoning (AOP). A total of 20 rabbits were divided into three groups: sham ($n = 8$), pralidoxime (PAM) + atropine ($n = 6$), and CoQ10 + PAM + atropine ($n = 6$). Blood samples were taken from each test subject to measure the values of acetylcholinesterase (AChE), nitric oxide (NO), and malondialdehyde (MDA) in the plasma and erythrocyte before administration of 50 mg/kg dichlorvos by orogastric tube. Blood samples were then taken at 1, 12, and 24 h post-dichlorvos to determine plasma and erythrocyte levels of AChE, NO, and MDA. Sham group received no treatment. PAM + atropine group received 0.05 mg/kg atropine with repeated doses and PAM: first a 30-mg/kg intravenous (IV) bolus, then a 15-mg/kg IV bolus every 4 h. CoQ10 + PAM + atropine group received same dose PAM and atropine and a 50-mg bolus of IV CoQ10. Thoracotomy was performed in all the animals 24 h after poisoning and then heart tissue samples were obtained. At 12 and 24 h, erythrocyte AChE levels in the CoQ10 animals were considerably higher than those in PAM + atropine animals ($p = 0.023$ and 0.017, respectively). At 12 and 24 h, erythrocyte MDA and NO levels in CoQ10 animals were significantly lower than those in PAM + atropine animals ($p < 0.05$). Heart tissue AChE levels in CoQ10 animals were considerably higher than those of the sham and PAM + atropine animals ($p = 0.001$). Heart tissue MDA and NO levels of CoQ10 animals were significantly lower than those of the sham and PAM + atropine animals ($p < 0.01$). Treatment of AOP with CoQ10 + PAM + atropine in this animal model had a beneficial effect on both erythrocyte and heart tissue lipid peroxidation and AChE activity.

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