Zehirlenmelerde Yeni Antidotlar

Dr. Y.Kemal GÜNAYDIN
Konya Eğitim ve Araştırma Hastanesi
Acil Tıp Kliniği

Antidot

- Zehri etkisizleştiren
- Zehrin etkisini önleyen
- Zehrin etkisini azaltan
- Panzehir vb…….

Antidot

- **ASLINDA;**
- Zehrin **toksikokinetik** ve **toksikodinamiğini** değiştirebilen
- Kullanımı güvenli
- Zehirlenen kişide yararlı etkileri kanıtlanmış maddeler

Tarihte Andidotlar

- Yunan mitolojisi, şifa tanrıçası Panacea'nın iksiri
- ***Tiryak***, evrensel antidot, vahşi hayvan anlamında
- Yaklaşık 40 çeşit antidot
- Nero'nun hekimi ***Andromachus'un macunu***
- ***Venedik Tiryakı***
- Roma döneminin tıp lideri Yunan hekim ***Galen'in Tiryakı***
- Anadolunun antidotu ***" Mesir Macunu"*** 41 değişik baharattan oluşur

Günümüzde Andidotlar

- ***Yetim ilaç (Orphan drug)*** durumundadır
- Üretim maliyetleri yüksek
- İlaç firmalarının ilgisi az
- Klinik araştırma oldukça zor
- İhtiyaca bağlı olarak üretimi gerçekleştiren ülkeden ithal edilir

Günümüzde Andidotlar

- ***Klinik araştırmalar çok nadir***
- Genellikle vaka serileri
- Hayvan çalışmaları
- Deneysel çalışmalar

Antidot

- Antidotlar hakkında bilgiler, uluslar arası organizasyonlar tarafından yayınlanır:

  WHO (World Health Organisation)

  UNEP (United Nations Environment Programme)

  ILO (International Labour Organisation)
- Türkiye'de sorumlu olan kurum 2001 yılından bu yana RSHM Başkanlığı Zehir Danışma Merkezi

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

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

Güncel Antidotlar

- İV Lipid Tedavisi
- İnsülin - glukoz
- Organofosfat (OP) zehirlenmelerinde yeni antidotlar
- Etil Alkol zehirlenmesinde zitramin
- Siyanur zehirlenmelerinde yeni antidotlar
- Mantar zehirlenmelerinde silibinin

İV Lipid Tedavisi

- Kalsiyum kanal blokörleri
- Beta-blokörler
- Trisiklik antidepresanlar
- Bupropion
- Lokal anestezikler
- Ketiapin
- Tramadol
- Flecainide
- Kokain

İV Lipid Tedavisi

- Kardiyovasküler kollaps kliniği olan zehirlenme hastalarının tedavisinde giderek artan şekilde kullanılmakta

- İleri kardiyak yaşam desteği algoritmalarında, beta blokör ve kalsiyum kanal blokörü zehirlenmelerine sekonder gelişen kardiyak arrest vakalarında resüsitasyonda önerilmekte.

Stellpflug SJ, et al. Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high-dose insulin. Clin Toxicol (Phila). 2010;48(3):227-229.

French D, et al. Serum verapamil concentrations before and after Intralipid® therapy during treatment of an overdose. Clin Toxicol (Phila). 2011;49(4):340-344.

LipidRescue™ Resuscitation...for drug toxicity. 2013; Available at: http://www.lipidrescue.org/. Accessed November 1, 2013. (Website)

Young AC, et al. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation. 2009;80(5):591-593.

İV Lipid Tedavisi

- Etki mekanizması ile ilgili 3 teori

  1- Mitokondriyal membrandan yağ asiti transportunu artırarak hücreye gerekli enerjininin oluşturulmasına olanak verir

  2- Kardiyak myositlerdeki Ca seviyelerini artırarak inotrop artışa neden olur

  3- Lipidde çüzünebilen ilaçların dengelenmesi yoluyla toksinlerin dokudan lipid solüsyonuna geçmesi

İV Lipid Tedavisi

- ***Yükleme dozu*** 1.5 mL/kg bolus, 2 - 3 dk'da
- ***İnfüzyon dozu*** 0.25 – 0.5 mL/kg/dk 60 dk
- ***Tekrar dozu*** Asistol/NEA durumunda ve ilk doz sonrasında iyileşme olmadıysa ya da hemodinami bozuk seyrediyorsa 3 doz tekrar edilebilir
- ***Max doz*** 10-12 mL/kg

ACMT position statement: interim guidance for the use of lipid resuscitation therapy. J Med Toxicol. 2011;7(1):81-82.

Intravenous lipid emulsion therapy. Trends in anaesthesia and critical care. 3 (2013), 336 - 341

İO Lipid Tedavisi

- Yapılan bir çalışmada bupivakain verilen radlarda İO lipid infüzyonu ile İV lipid infüzyonu arasında etkinlik açısından bir fark bulamamışlar.

Intraosseous Lipid Emulsion: An Effective Alternative to IV Delivery in Emergency Situations. Fettiplace, Michael; Ripper, Richard; Lis, Kinga; Feinstein, Douglas; Rubinstein, Israel; Weinberg, Guy Critical Care Medicine. 42(2):e157-e160, February 2014.

İV Lipid Komplikasyonları

- Pankreatit
- Bronkospazm
- ARDS
- Laboratuvar bulgularında değişiklikler
- Vasküler komplikasyonlar

THE ASSOCIATION OF ANAESTHETISTS

of Great Britain & Ireland

Guidelines for the Management of Severe Local Anaesthetic Toxicity

Signs of severe toxicity:

- Sudden loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
- Local anaesthetic (LA) toxicity may occur some time after the initial injection

Immediate management:

- Stop injecting the LA
- **Call for help**
- Maintain the airway and, if necessary, secure it with a tracheal tube
- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Assess cardiovascular status throughout

Management of cardiac arrest associated with LA injection:

- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that they may be very refractory to treatment
- Prolonged resuscitation may be necessary; it may be appropriate to consider other options:
  - **Consider the use of cardiopulmonary bypass if available**
  - **Consider treatment with lipid emulsion**

Treatment of cardiac arrest with lipid emulsion: (approximate doses are given in red for a 70-kg patient)

- Give an intravenous bolus injection of Intralipid® 20% 1.5 ml.kg^{-1} over 1 min
  - Give a bolus of 100 ml
- Continue CPR
- Start an intravenous infusion of Intralipid® 20% at 0.25 ml.kg^{-1}.min^{-1}
  - Give at a rate of 400 ml over 20 min
- Repeat the bolus injection twice at 5 min intervals if an adequate circulation has not been restored
  - Give two further boluses of 100 ml at 5 min intervals
- After another 5 min, increase the rate to 0.5 ml.kg^{-1}.min^{-1} if an adequate circulation has not been restored
  - Give at a rate of 400 ml over 10 min
- Continue infusion until a stable and adequate circulation has been restored

Trends in Anaesthesia and Critical Care 3 (2013) 336–341

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REVIEW

Intravenous lipid emulsion therapy – The fat of the land

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Keywords:
Intravenous lipid emulsion
Local anaesthetic toxicity
Calcium channel antagonist overdose
Tri-cyclic antidepressant overdose

S U M M A R Y

Local anaesthetic agents are utilised ubiquitously in clinical practice, and as such potentially grave adverse events such as systemic toxicity can occur. Although the use of ultrasound, and nerve stimulator guided administration have reduced the risk of such adversities, they unfortunately have not been eliminated. This review examines the pharmacology and toxicology of local anaesthetic agents and the use of Intravenous Lipid Emulsion (ILE) to counteract the systemic toxic effects. The research underpinning the 'Lipid Sink' and 'Lipid Flux' theories of ILE mechanism of action are explored, as is the novel and successful use of ILE in other lipophilic drug toxidromes, such as overdoses of tri-cyclic antidepressants and calcium channel antagonists. Also discussed are the potential direct and indirect risks associated with the use of intravenous lipid treatments and the possibility for reporting bias in the literature. Despite this, case reports of the successful use of ILE are certainly compelling, and have led to the rapid adoption of ILE in clinical practice and the recommendation for its use by anaesthetic associations worldwide.

6. Complications of intravenous lipid emulsion

Paracelsus has previously written 'all things are poison, and nothing is without poison; only the dose permits something not to be poisonous'. This may run true with ILE therapy, as previous studies have shown large volumes of high concentration of lipid infusion during parenteral nutrition have resulted in pulmonary complications.[13] Furthermore there are some theoretical and animal experimental data which highlight some of the risks associated with ILE therapy. Studies in rodents have shown reduced resistance to bacterial pathogens with parenteral lipid administration.[50] However, part of the explanation may be due to the experimental methodology as a parenteral lipid infusion is likely to have a greater risk of bacterial contamination/colonisation than saline infusions. Furthermore some of the infective risks associated with parenteral lipid infusion may be related to the long duration of infusions over days-weeks, in contrast ILE therapy is an infusion utilised for minutes to hours.

A systematic review of lipid therapy for acute drug poisoning in animal and human studies reported that although there is some benefit of ILE utilisation in certain drug toxicities, the evidence is weak, with human data based on case reports. Furthermore it found no trials examining the safety of ILE in acute poisoning.[51] However, whilst there has been one case report detailing the occurrence of asymptomatic hyperamylasemia post ILE use, most authors have not reported any adverse events associated with lipid therapy.[52] Nevertheless, the AAGBI recommend the monitoring of the patient and biochemical markers for the development of pancreatitis post treatment with intravenous lipids.

The maximum dose that can be administered to humans is unknown; experiments in rats have shown the lethal dose required to kill 50% of the animals (LD50) to be 68 ml/kg of rapidly infused 20% intravenous lipid.[53] In humans, the recommended upper limit of 20% intravenous lipid is 10 ml/kg.[51]

7. Conclusion

Throughout this article we have chronicled the use of intravenous lipid emulsion, from its serendipitous inception to ever accumulating case reports of successful resuscitation in current clinical practice. Not only does ILE have demonstrable efficacy as an antidote to local anaesthetic toxicity, its spectrum of use now clearly lies beyond this to encompass the treatment of other lipid soluble drug toxidromes. While the mechanism of action is not clearly elucidated, we surmise that the high dose lipid leaches the toxic drug from inactivated ion channels - either by reducing the intravenous drug concentration or directly from the ion channels themselves. No doubt, as clinical familiarity and confidence with its use continues to grow, we expect to see more case reports of successful resuscitation from the use of intravenous lipid emulsion.

doi: 10.1111/j.1742-6723.2011.01398.x *Emergency Medicine Australasia* (2011) 23, 123–141

EMA

REVIEW ARTICLE

Review article: Intravenous lipid emulsion as antidote: A summary of published human experience

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Abstract

Intravenous lipid emulsion (ILE) has been demonstrated to be effective in amelioration of cardiovascular and central nervous system sequelae of local-anaesthetic and non-local-anaesthetic drug toxicity in animal models. Sequestration of lipophilic toxins to an expanded plasma lipid phase is credited as the predominant beneficial mechanism of action of ILE. Systematic review of published human experience is however lacking. We determined to report a comprehensive literature search of all human reports of ILE application in drug poisoning. Forty-two cases of ILE use (19 local-anaesthetic, 23 non-local-anaesthetic) were identified, with anecdotal reports of successful resuscitation from cardiovascular collapse and central nervous system depression associated with ILE administration in lipophilic toxin overdose. Although significant heterogeneity was observed in both agents of intoxication, and reported outcomes; case report data suggest a possible benefit of ILE in potentially life-threatening cardio-toxicity from bupivacaine, mepivacaine, ropivacaine, haloperidol, tricyclic antidepressants, lipophilic beta blockers and calcium channel blockers. Further controlled study and systematic evaluation of human cases is required to define the clinical role of ILE in acute poisonings.

Conclusion

Despite the ever-increasing case report literature of the use of lipid emulsion therapy in poisoning, the absolute indications for its use remain limited. ILE might be considered in severe cardiovascular instability resulting from lipophilic toxin poisoning, in particular if this does not respond to conventional measures. ILE cannot currently be recommended as a therapy for the sole reason of a reduced level of consciousness. Further scientific guidance, in the form of pre- and post-ILE administration serum drug concentrations in individual cases, and clinical outcome trials in the general toxicology population will assist greatly in determining the role and effectiveness of ILE therapy in poisoning.

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healthcare

RESEARCH ARTICLE

Hypertonic sodium bicarbonate versus intravenous lipid emulsion in a rabbit model of intravenous flecainide toxicity: no difference, no sink

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Context. The use of intravenous lipid emulsion (ILE) as an antidote in non-local, anaesthetic drug toxicity has generated considerable interest. Flecainide is a lipophilic anti-arrhythmic with a significant cardiotoxic profile, with blockade of sodium and potassium channels causing arrhythmias and shock in severe toxicity. ILE has been proposed as a treatment option in severe flecainide toxicity refractory to other modalities. *Objective.* We compared the effects of ILE and hypertonic sodium bicarbonate in a rabbit model of flecainide toxicity. *Materials and methods.* Twenty sedated and ventilated New Zealand White Rabbits received flecainide infusion titrated to a mean arterial pressure (MAP) of 60% baseline, which was defined as toxicity. The rabbits then received either sodium bicarbonate or ILE, and the flecainide infusion was reduced in an attempt to model ongoing enteric absorption. MAP and heart rate were recorded every minute for 15 min and plasma flecainide concentration was measured at toxicity and 15 min. ECG QRS duration was recorded at baseline, toxicity and at 5, 10 and 15 min post-toxicity. *Results.* No difference was observed in heart rate ($p = 0.2804$), MAP ($p = 0.1802$) or QRS duration ($p = 0.7471$) between groups. The immediate rate of rise in MAP was greatest in the bicarbonate group in the 5 min immediately post-toxicity. *Conclusions.* In this study, no differences were observed between an active control of hypertonic sodium bicarbonate and ILE for the primary endpoint of MAP at 15 min nor for QRS duration at any timepoint. There was a transient rapid increase in blood pressure seen in the sodium bicarbonate group that was not sustained. No increase was seen in blood concentration of flecainide in the ILE group, suggesting no 'lipid sink' for flecainide in this model. More research is warranted to define any role for ILE in flecainide toxicity.

Keywords Sodium Bicarbonate; Lipid Emulsions; intravenous; Flecainide; Toxicity; Antidote

İnsülin - Glukoz

- Ciddi anstabil KKB ve BB zehirlenmelerinin tedavisinde etkin
- İnsülinin kalbi metabolik olarak hücre düzeyinde koruduğu düşünülmekte
- Kalp hücreleri içine glukoz reuptakeni 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.

İnsülin - Glukoz

- ***Yükleme dozu*** 0.5 - 1 U/kg bolus regüler insülin ve 25 gr dekstroz
- ***İnfüzyon dozu*** 0.5 - 1 U/kg/sa regüler insülin ve 0.5 g/kg/sa dekstroz
- Kan şekeri ve K yakın takip

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RESEARCH ARTICLE

A blinded, randomized, controlled trial of three doses of high-dose insulin in poison-induced cardiogenic shock

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Background. High dose insulin (HDI) has proven superior to glucagon and catecholamines in the treatment of poison-induced cardiogenic shock (PICS) in previous animal studies. Standard recommendations for dosing of insulin vary and the optimal dose of HDI in PICS has not been established. Our hypothesis was a dose of 10 U/kg/hr of HDI would be superior to 1 U/kg/hr with cardiac output (CO) as our primary outcome measure in pigs with propranolol-induced PICS. *Methods.* This was a blinded, prospective, randomized trial with 4 arms consisting of 4 pigs in each arm. The arms were as follows: placebo (P), 1 U/kg/hr (HDI-1), 5 U/kg/hr (HDI-5), and 10 U/kg/hr (HDI-10). Cardiogenic shock was induced with a bolus of 0.5 mg/kg of propranolol followed by an infusion of 0.25 mg/kg/min until the point of toxicity, defined as 0.75 x (HR x MAP) was reached. At this point the propranolol infusion was decreased to 0.125 mg/kg/min and a 20 mL/kg bolus of normal saline (NS) was administered. The protocol was continued for 6 hours or until the animals died. *Results*. 2 pigs died in the P arm, 1 pig died each in the HDI-1 and HDI-5 arms, and all pigs lived in the HDI-10 arm. There was a statistically significant difference in dose by time interaction on CO of 1.13 L/min over the 6 hr study period ($p = < 0.001$). There was also a statistically significant difference in dose by time interaction on MAP, HR, and systemic vascular resistance (SVR). No statistically significant difference was found between any of the arms regarding glucose utilization. *Conclusion.* HDI was statistically and clinically significantly superior to placebo in this propranolol model of PICS. Furthermore a dose response over time was found where CO increased corresponding to increases in doses of HDI.

Keywords High dose insulin; Cardiogenic shock; Beta blockers

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0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2013.08.135

Selected Topics: Toxicology

HIGH-DOSE INSULIN AND INTRAVENOUS LIPID EMULSION THERAPY FOR CARDIOGENIC SHOCK INDUCED BY INTENTIONAL CALCIUM-CHANNEL BLOCKER AND BETA-BLOCKER OVERDOSE: A CASE SERIES

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☐ Abstract—Background: Recently, high-dose insulin (HDI) and intravenous lipid emulsion (ILE) have emerged as treatment options for severe toxicity from calcium-channel blocker (CCB) and beta blocker (BB). Objective: Our aim was to describe the use and effectiveness of HDI and ILE for the treatment of CCB and BB overdose. Case Reports: We describe 2 patients presenting to the emergency department after intentional ingestions of CCBs and BBs. A 35-year-old man presented in pulseless electrical activity after ingesting amlodopine, verapamil, and metoprolol. A 59-year-old man presented with cardiogenic shock (CS) after ingesting amlodopine, simvastatin, lisinopril, and metformin. Both patients were initially treated with glucagon, calcium, and vasopressors. Shortly after arrival, HDI (1 unit/kg × 1; 1 unit/kg/h infusion) and ILE 20% (1.5 mL/kg × 1; 0.25 mL/kg/min × 60 min) were initiated. This led to hemodynamic improvement and resolution of shock. At the time of hospital discharge, both patients had achieved full neurologic recovery. Conclusions: HDI effectively reverses CS induced by CCBs and BBs due to its inotropic effects, uptake of glucose into cardiac muscle, and peripheral vasodilatation. ILE is theorized to sequester agents dependent on lipid solubility from the plasma, preventing further toxicity. To our knowledge, these are the first two successful cases reported using the combination of HDI and ILE for reversing CS induced by intentional ingestions of CCBs and BBs.

☐ Keywords—high-dose insulin; lipid emulsion; overdose; beta blocker; calcium-channel blocker

OP zehirlenmelerinde yeni antidotlar

- Yeni oksimler
- Magnezyum Sülfat
- NaHCO3
- Antioksidanlar
- Anisodamin
- OP Hidrolaz

REVIEW

New experimental Oximes in the management of organophosphorus pesticides poisoning

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ABSTRACT

Organophosphorus compounds (OPCs) are widely used in agriculture as pesticides and occasionally in industrial settings. They have also been developed as warfare nerve agents. OPCs poisoning from intentional, accidental, and occupational exposure is a major public health problem, especially across the rural developing world. The main toxic mechanism of OPCs is the inhibition of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), resulting in accumulation of acetylcholine (ACh) at the synapse with cholinergic crisis and possible death. Exposure to even small amounts of an OPC can be fatal and death is usually caused by respiratory failure. Standard treatment involves the administration of intravenous atropine and an oxime to counteract acetylcholinesterase inhibition at the synapse, but the usefulness of oximes is still debated. During more than five decades, pyridinium oximes have been developed as therapeutic agents used in the medical treatment of poisoning with OPCs. They act by reactivation of AChE inhibited by OPCs. However, their activity in poisonings with pesticides and warfare nerve agents is different, and there is still no universal oxime sufficiently effective against all known OPCs. The aim of this article was to review the most recent findings in this field and compare the protection conferred by the new K-oximes and sugar oximes with the effect of the four recommended pyridinium oximes (pralidoxime, obidoxime, trimedoxime, and HI-6), in the search for a broad-spectrum AChE reactivator. *(Minerva Anestesiol 2011;77:1197-1203)*

Key words: Oximes - Organophosphorus compounds - Cholinesterase reactivators.

OP – Yeni Oksimler

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

Drug development for the management of organophosphorus poisoning

Paul Wilhelm Elsinghorst, Franz Worek, Horst Thiermann & Timo Wille†
Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany

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.

Keywords: bioscavenger, cyclodextrins, organophosphorus poisoning, oximes

Expert Opin. Drug Discov. (2013) 8(12):1467-1477

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

OP - NaHCO3

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

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OP – E Vitamini

- OP zehirlenmeleri dokularda oksijen radikalleri birikimine yol açar
- Ratlar üzerinde yapılan çalışmalarda E vitamininin OP zehirlenmelerinin neden olduğu oksidatif hasarı önlediği görülmüş.

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OP – Mg Sülfat

- 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 gereksinimini azaltır
- Ancak rutin kullanıma girmesi için daha fazla çalışmalar gerekli

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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

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
- Bugünlerde FDA onayı almaya çalışılıyor

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Article

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Can anisodamine be a potential substitute for high-dose atropine in cases of organophosphate poisoning?

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Abstract

A case of organophosphate (OP) poisoning was admitted to the emergency room. The patient accepted treatment with pralidoxime (PAM), atropine, and supporting therapy. It was observed that even after 22 h after treatment, 960 mg of atropine was not enough for the patient to be atropinized. However, a 160-mg follow-up treatment of anisodamine was quite enough for atropinization after 4 h. As a case report, more studies are required before any definite conclusion can be reached regarding the use of anisodamine as a potential substitute for high-dose atropine in cases of OP poisoning.

Keywords

Organophosphate poisoning, atropine, atropinization, anisodamine

As shown in this case, atropinization was achieved through the administration of a total atropine dose of 960 mg over 22 h with concomitant administration of 480 mg of anisodamine over 4 h. Anisodamine is a kind of acetylcholine receptor-blocking drug with the pharmacological mechanism of atropine. With peripheral anticholinergic effects, it can relax the spasm of smooth muscles and microvascular tissues and improve the rigidity and tremor symptoms. Thus, as a calcium channel blocker, it can inhibit Ca^{2+} influx.[5] It was unclear why anisodamine brought about atropinization more quickly than atropine. On the one hand, OPs are fat-soluble compounds that can rapidly spread in tissues and easily pass through the blood–brain barrier, allowing them to exert their effects on the central nervous system,[6] and anisodamine has the ability to preferentially interact with acidic membrane phospholipids, which would serve to protect nerve cells.[7] On the other hand, the patient was constitutionally resistant to atropine but was sensitive to anisodamine. Therefore, it is reasonable to believe that a high dose of atropine may not be what is needed when a patient is judged to be atropine resistant. More clinical data are needed to ascertain whether anisodamine can be used in place of high doses of atropine in such patients.

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BIOCHEMISTRY, BIOPHYSICS AND MOLECULAR BIOLOGY

Zitramin—A New Antidote for Acute Ethanol Intoxication

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Zitramin

- İntragastrik olarak etanol verilen ratlar üzerinde deneysel bir hayvan çalışması
- Plasebo kontrollü bir çalışma
- 18 rat
- Zitramin bir organik çinko derivesi
- Zitraminin KCFT'nin düşürülmesinde etkili olduğu görülmüş
- Etanol intoksikasyonunda kullanılması için klinik çalışmalara ihtiyaç olduğu vurgulanmış.

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RESEARCH ARTICLE

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

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Context. Cyanide is a component of smoke in residential and industrial fires, and accidental exposure to cyanide occurs in a variety of industries. Moreover, cyanide has the potential to be used by terrorists, particularly in a closed space such as an airport or train station. Current therapies for cyanide poisoning must be given by intravenous administration, limiting their use in treating mass casualties. *Objective.* We are developing two new cyanide antidotes – cobinamide, a vitamin B_{12} analog, and sulfanegen, a 3-mercaptopyruvate prodrug. Both drugs can be given by intramuscular administration, and therefore could be used to treat a large number of people quickly. We now asked if the two drugs would have an augmented effect when combined. *Materials and methods.* We used a non-lethal and two different lethal models of cyanide poisoning in mice. The non-lethal model assesses neurologic recovery by quantitatively evaluating the innate righting reflex time of a mouse. The two lethal models are a cyanide injection and a cyanide inhalation model. *Results.* We found that the two drugs are at least additive when used together in both the non-lethal and lethal models: at doses where all animals died with either drug alone, the combination yielded 80 and 40% survival in the injection and inhalation models, respectively. Similarly, drug doses that yielded 40% survival with either drug alone, yielded 80 and 100% survival in the injection and inhalation models, respectively. As part of the inhalation model, we developed a new paradigm in which animals are exposed to cyanide gas, injected intramuscularly with an antidote, and then re-exposed to cyanide gas. This simulates cyanide exposure of a large number of people in a closed space, because people would remain exposed to cyanide, even after receiving an antidote. *Conclusion.* The combination of cobinamide and sulfanegen shows great promise as a new approach to treating cyanide poisoning.

Keywords Inhalation exposure; Intramuscular injection; Lethal model; Non-lethal model

Article

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Supramolecular ferric porphyrins and a cyclodextrin dimer as antidotes for cyanide poisoning

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Abstract

Objectives: This study aimed to evaluate the antidotal effect of a newly developed supramolecular complex, ferric porphyrins and a cyclodextrin dimer (Fe^{III}PIm3CD), that possess a higher binding constant and quicker binding rate to cyanide ions than those of hydroxocobalamin (OHCbl) in the presence of serum protein. **Methods:** First, in vitro cytochrome activity and cell viability were evaluated in murine fibroblast cells cultured with various doses of Fe^{III}PIm3CD and potassium cyanide (KCN). Next, BALB/c mice were pretreated with intravenous OHCbl (0.23 mmol/kg), Fe^{III}PIm3CD (0.23 mmol/kg), or saline and then received KCN (lethal dose 100% (LD_{100}): 0.23 mmol/kg) through a stomach tube. Finally, as a resuscitation model, KCN-induced apnea was treated with a bolus injection of an equimolar dose of antidotes followed by a slow infusion of the same reagent. **Results:** Fe^{III}PIm3CD showed dose-dependent antidotal effects in vitro. Pretreatment with Fe^{III}PIm3CD prevented KCN-induced apnea significantly better than OHCbl. Resuscitation with Fe^{III}PIm3CD resulted in an earlier resumption of respiration than that seen with OHCbl. However, 24-h survival was similar among the treatments (Fe^{III}PIm3CD, nine of nine mice; OHCbl, eight of nine mice). **Conclusion:** Fe^{III}PIm3CD exerted significant antidotal effects on cyanide toxicity in vitro and in vivo, with a potency equal in the mortality of cyanide-poisoned mice or superior in the respiratory status during an acute phase to those of OHCbl.

Keywords

Cyanide, imidazole linker, hydroxocobalamin, antidote

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.

Current Pharmaceutical Biotechnology, 2012, *13*, 1964-1970

Legalon® SIL: The Antidote of Choice in Patients with Acute Hepatotoxicity from Amatoxin Poisoning

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Abstract: More than 90% of all fatal mushroom poisonings worldwide are due to amatoxin containing species that grow abundantly in Europe, South Asia, and the Indian subcontinent. Many cases have also been reported in North America. Initial symptoms of abdominal cramps, vomiting, and a severe cholera-like diarrhea generally do not manifest until at least six to eight hours following ingestion and can be followed by renal and hepatic failure. Outcomes range from complete recovery to fulminant organ failure and death which can sometimes be averted by liver transplant. There are no controlled clinical studies available due to ethical reasons, but uncontrolled trials and case reports describe successful treatment with intravenous silibinin (Legalon® SIL). In nearly 1,500 documented cases, the overall mortality in patients treated with Legalon® SIL is less than 10% in comparison to more than 20% when using penicillin or a combination of silibinin and penicillin. Silibinin, a proven antioxidative and anti-inflammatory acting flavonolignan isolated from milk thistle extracts, has been shown to interact with specific hepatic transport proteins blocking cellular amatoxin re-uptake and thus interrupting enterohepatic circulation of the toxin. The addition of intravenous silibinin to aggressive intravenous fluid management serves to arrest and allow reversal of the manifestation of fulminant hepatic failure, even in severely poisoned patients. These findings together with the available clinical experience justify the use of silibinin as Legalon® SIL in *Amanita* poisoning cases.

Keywords: *Amanita phalloides* poisoning, Amatoxin, Acute Hepatic Failure, Antidote, Legalon® SIL, Silibinin.

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Amanita phalloides poisoning and treatment with silibinin in the Australian Capital Territory and New South Wales.

OBJECTIVES: To report the frequency and clinical outcomes of Amanita phalloides poisoning in the Australian Capital Territory and New South Wales, and the treatments used (including silibinin).

DESIGN,SETTING AND PATIENTS: Retrospective case series of patients admitted to public hospitals in Canberra and Sydney for suspected A. phalloides poisoning between 1999 and 2012 (identified from hospital records and calls to the New South Wales Poisons Information Centre).

MAIN OUTCOME MEASURES: Frequency of poisoning and the clinical outcomes.

RESULTS: Twelve patients presented with a history suggesting A. phalloides poisoning, 10 with probable poisoning and two with possible poisoning. Eight of those with probable poisoning developed significant hepatotoxicity and four died. Silibinin was administered to nine of those with probable poisoning (the other presented before 2005). Maintaining silibinin supply became a challenge during two clusters of poisoning. Eight of the patients with probable poisoning were not long-term residents of the ACT, and six were immigrants from Asia.

CONCLUSIONS: The mortality rate due to A. phalloides poisoning in this case series was high despite treatment according to current standards, including use of silibinin, and the frequency of hepatotoxicity was more than double that for the previous decade. Ongoing public health campaigns are required.