Zehirlenmelerde yeni antidotlar ve lipit tedavisi

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Plan

Antidot?
– Güncel antidotlar
– Yeni antidotlar ????
– Antidotların yeni kullanımı
Intra venöz lipid emulsiyonları
– Hangi ilaçlar
– Etki mekanizması
– Lipid solusyonları
– Dozlar ve komplikasyonlar

Antidot

“Zehri etkisizleştiren”
“Zehrin etkisini önleyen”
“Zehrin etkisini ortadan kaldırabilme özelliği olan madde, panzehir”
“Zehrin etkisini azaltan, etkisini tersine çeviren, zehirsizleştirme”

+ =

1- Türk Dil Kurumu, Güncel Türkçe Sözlük, http://www.tdk.gov.tr/ Erişim: Aralık 2012.

2- Baydar T, Palabıyık S, Girgin G. Antidot: kavramlar ve sınıfl amalar. Hacettepe Tıp Dergisi. 2010; 41:105-112

Hangi antidotlar

12 a
– At
– Ka
– Siyanid antidot kiti veya
hi
– Dig
– Flu
– Glu
– Met
– Nal
– Fiz
– Pri
–Sodyum bikarbonat

– Polivalan Yılan antivenomu

nu

TOXICOLOGY/CONCEPTS

Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care

Study objective: We developed recommendations for antidote stocking at hospitals that provide emergency care.

Methods: An expert panel representing diverse perspectives (clinical pharmacology, clinical toxicology, critical care medicine, clinical pharmacy, emergency medicine, internal medicine, pediatrics, poison centers, pulmonary medicine, and hospital accreditation) was formed to create recommendations for antidote stocking. Using a standardized summary of the medical literature, the primary reviewer for each antidote proposed guidelines for antidote stocking to the full panel. The panel used a formal iterative process to reach their recommendation for the quantity of an antidote that should be stocked and the acceptable period for delivery of each antidote.

Results: The panel recommended consideration of 24 antidotes for stocking. The panel recommended that 12 of the antidotes be available for immediate administration on patient arrival. In most hospitals, this period requires that the antidote be stocked in the emergency department. Another 9 antidotes were recommended for availability within 1 hour of the decision to administer, allowing the antidote to be stocked in the hospital pharmacy if the hospital has a mechanism for prompt delivery of antidotes. The panel identified additional antidotes that should be stocked by the hospital but are not usually needed within the first hour of treatment. The panel recommended that each hospital perform a formal antidote hazard vulnerability assessment to determine the need for antidote stocking in that hospital.

Conclusion: The antidote expert recommendations provide a tool to be used in creating practices for appropriate and adequate antidote stocking in hospitals that provide emergency care. [Ann Emerg Med. 2009;54:386-394.]

Ann Emerg Med 2009;54:386

Ulusal zehir danışma (önerdiği) antidot listesi

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

Yeni antidot?

Etik uygulamalarda zorluk

↓

Zehirlenmeler ilaç firmalarının ilgisini çekecek kadar cazip değil

↓

Antidotlar yetim ilaçlardır.. (orphan drug)

↓

Bu nedenle yeni antidot az/yok

Yeni antidotlar

Karnitin

İnsülin - glukoz

Organofosfat (OP) -yeni antidotlar

Siyanür-Sülfür Donörleri

Yeni kuşak oral antikoagülanlar

İV Lipid Tedavisi

Karnitin Valproik asid zehirlenmelerinde kullanılmakta

KKB zehirlenmesinde ffa hepatik oksidasyonu ve reuptake↑

İnsulin rezistansını↓

Hayvan çalışmalarında MAP ve surveyi ↑

...asing insulin resistance, promoting intracellular glucose transport, facilitating the metabolism of free fatty acids, and increasing calcium channel sensitivity. It may have also stimulated oxidative utilization of glucose instead of converting pyruvate into lactate and contributed to decrease lactate production with metformin poisoning.

KlineJA,(1996)Myocardialmetabolism during gradedintra portalverapami linfusion in a wakedogs.JCardiovascPharm27:719–726
PerezE, (2011) L-Carnitine increases survival in a murine model of severe verapamil toxicity.AcadEmergMed18:1135–1140

Ciddi anstabil KKB ve BB zehirlenmelerinde

- insülin pozitif inotrop etkisini miyokardın stres anında kullandığı glukozun kullanımını kolaylaştır
- Kalp hücreleri içine glukoz reuptakeni arttırır
- NO üzerinden VD etki ile vasküler rezistansı azaltarak kardiyak outputu arttırır

HIET should begin with an i.v. loading dose of 1 unit/kg of regular insulin followed by an infusion of 0.5–1 unit/kg/hr.[39] The infusion dosage can be increased every 20–30 minutes. Doses of 2.5–3 units/kg/hr have been used depending on the response. Experimental studies have used even higher doses.[40] Serum glucose should be maintained at a concentration of >100 mg/dL during HIET. A maximum insulin dose has not been established. If the initial blood glucose concentration is <400 mg/dL, an i.v. loading dose of 0.5 g/kg dextrose should be administered with the insulin and followed by an infusion of 0.5 g/kg/hr of dextrose, with meticulous and frequent monitoring of serum glucose and potassium concentrations.[39] This dose of dextrose can be administered in a concentrated form (e.g., a 20–25% concentration) through a central line to avoid problems with fluid overload and venous irritation. The recommended goal is to maintain a serum glucose concentration of 100–250 mg/dL. A patient with a falling glucose concentration should be treated by increasing the amount of supplemental glucose (not by decreasing the insulin infusion) until the patient is hemodynamically stable.

Espinoza TR. Hyperinsulin therapy for calcium channel antagonist poisoning: a seven-year retrospective study.Am J Ther. 2013 Jan;20(1):29-31

Antidotes for toxicological emergencies: A practical review Am J Health-Syst Pharm—Vol 69 Feb 1, 2012

Hindawi Publishing Corporation
Case Reports in Critical Care
Volume 2012, Article ID 927040, 5 pages
doi:10.1155/2012/927040

Management of Calcium Channel Antagonist Overdose with Hyperinsulinemia-Euglycemia Therapy: Case Series and Review of the Literature

Table 1: Case reports of calcium channel antagonist overdose using hyperinsulinemia therapy with clinical outcomes.

CCA ingested	Dose range (mg)	Number of patients (%)	Insulin bolus (IU/kg)	Insulin infusion (IU/kg/hr)	Duration of treatment	Survival *N* (%)
Verapamil	2000–5800	10 (40)	0–1000 units (no IU/kg reported)	0-1	8–33 hours	9 (90)
Diltiazem	900–10080	9 (24)	0-1	0.2–1.5	6–8 hours	6 (67)
Amlodipine	30–1000	9 (36)	0-1	0–2.64	6–49 hours	8 (88)

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3. Conclusion

CCA poisoning is on the rise due to increased use for a number of cardiovascular indications. CCA overdose, whether intentional or accidental, can be lethal. HIE therapy has been shown to be beneficial in multiple animal studies as well as the majority of case series. HIE therapy should be considered early in the presentation of CCA toxicity in order to improve cardiac contractility and hemodynamics. Close monitoring of serum glucose and electrolytes is advised to prevent potential adverse effects.

Organofosfatlar

Yeni oksimler

Magnezyum Sülfat

$NaHCO_3$

Antioksidanlar

TDP

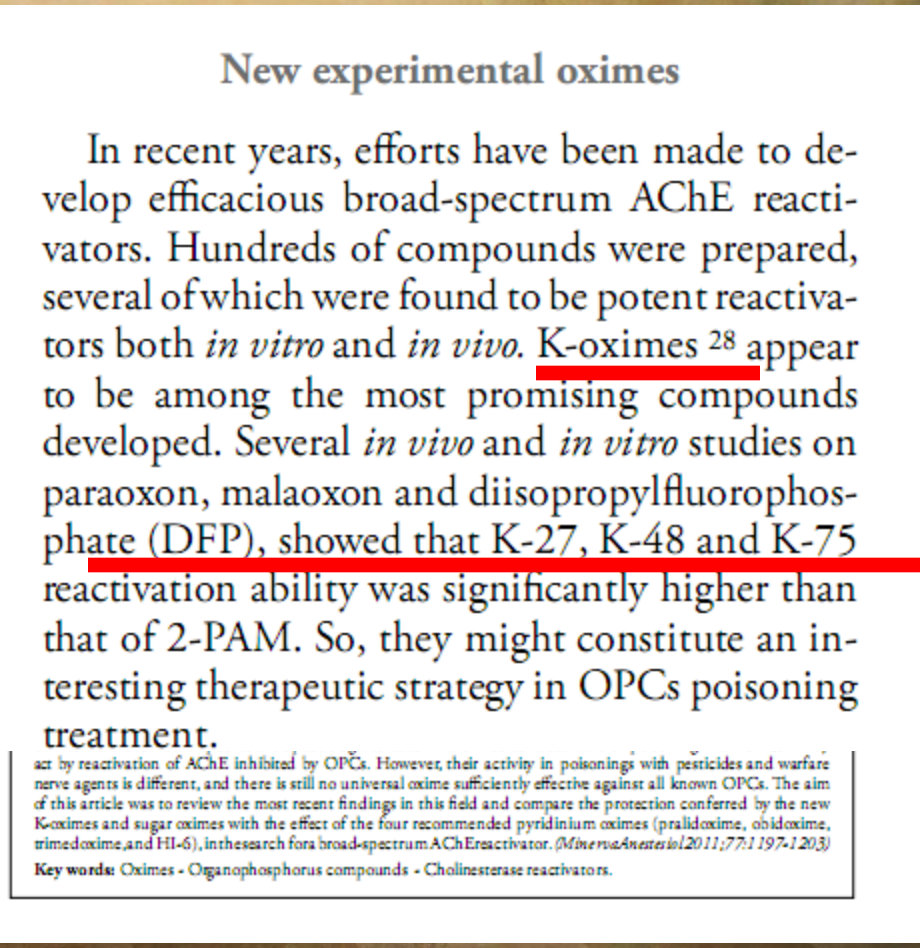
İLE

Balali-Mood M Recent advances in the treatment of organophosphorous poisonings. Iran J Med Sci. 2012 Jun;37(2):74-91.

OP – Yeni Oksimler

OKSİMLER

- Pralidoksim tüm dünyada en yaygın kullanılan
- Trimedoxime (TMB-4) ve obidoxime chloride (HI-6) askeri kullanım
- K-oksimlerin (K-27, K-48, K-53, K-74, K-75, K-107, K-108, and K-113) hayvan çalışmalarında AChE reaktivasyonunda PAM'dan daha etkili
- Kullanımlarına dair yeterli kanıt yok
- Daha fazla çalışma yapılmalı



New experimental oximes

In recent years, efforts have been made to develop efficacious broad-spectrum AChE reactivators. Hundreds of compounds were prepared, several of which were found to be potent reactivators both *in vitro* and *in vivo*. K-oximes [28] appear to be among the most promising compounds developed. Several *in vivo* and *in vitro* studies on paraoxon, malaoxon and diisopropylfluorophosphate (DFP), showed that K-27, K-48 and K-75 reactivation ability was significantly higher than that of 2-PAM. So, they might constitute an interesting therapeutic strategy in OPCs poisoning treatment.

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.

Buckley, Oximes for acute organophosphate pesticidepoisoning. Cochrane Database Syst Rev 2011
Barelli A,New experimental Oximes in the management of organophosphorus pesticides poisoning. Minerva Anestesiol. 2011

Siyanür-Sülfür Donörleri

Antidot kitleri
1- siyanüre bağlanma
2- methb'i indükleme
metHb: Hb'deki ferröz (Fe+2) →ferrik (Fe+3)
(siyanür için alternatif bağlanma alanı)
Siyanür+metHb→ siyanometHb (görece az toksik)
3- sülfür donörü

Dimetil trisülfür (DMTS), metil propil trisülfür (MPTS)

amp) IV

Siyanür zehirlenme tedavisinde kullanılan antidotlar.

Antidot	Uyg.yolu	Doz	Yan etki
Amil nitrit	inhalasyon	15-30 sn. inhalasyon arada 30 sn. dinlendirerek 1 kapsül 2-3 dk. uygulanır	methemoglobinemi vazodilatasyon başağrısı
Sodyum nitrit	iv	300 mg Çocuk % 3'lük solusyonundan 0.15-0.33 ml/kg maksimum 10 ml 4 dk. süreyle infüzyon	fatal methemoglobinemi
Sodyum toyosülfat	İv	12.5 g çocuk %25'lik çözeltiden 1.65 ml/kg Maksimum 50 ml 10 dk.dan az olmayan yavaş infüzyon	bulantı kusma kaslarda kramp artıralji
Hidrokso kobalamin	iv	4-5 g	Ürtiker, taşifilaksi
Dikobalt EDTA	iv	4 mg/kg	kobalt intoksikasyonu anafilaksi, hipotansiyon anjiyoödem
4 DMAP	im		methemoglobinemi

Identification, solubility enhancement and *in vivo* testing of a cyanide antidote candidate

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ABSTRACT

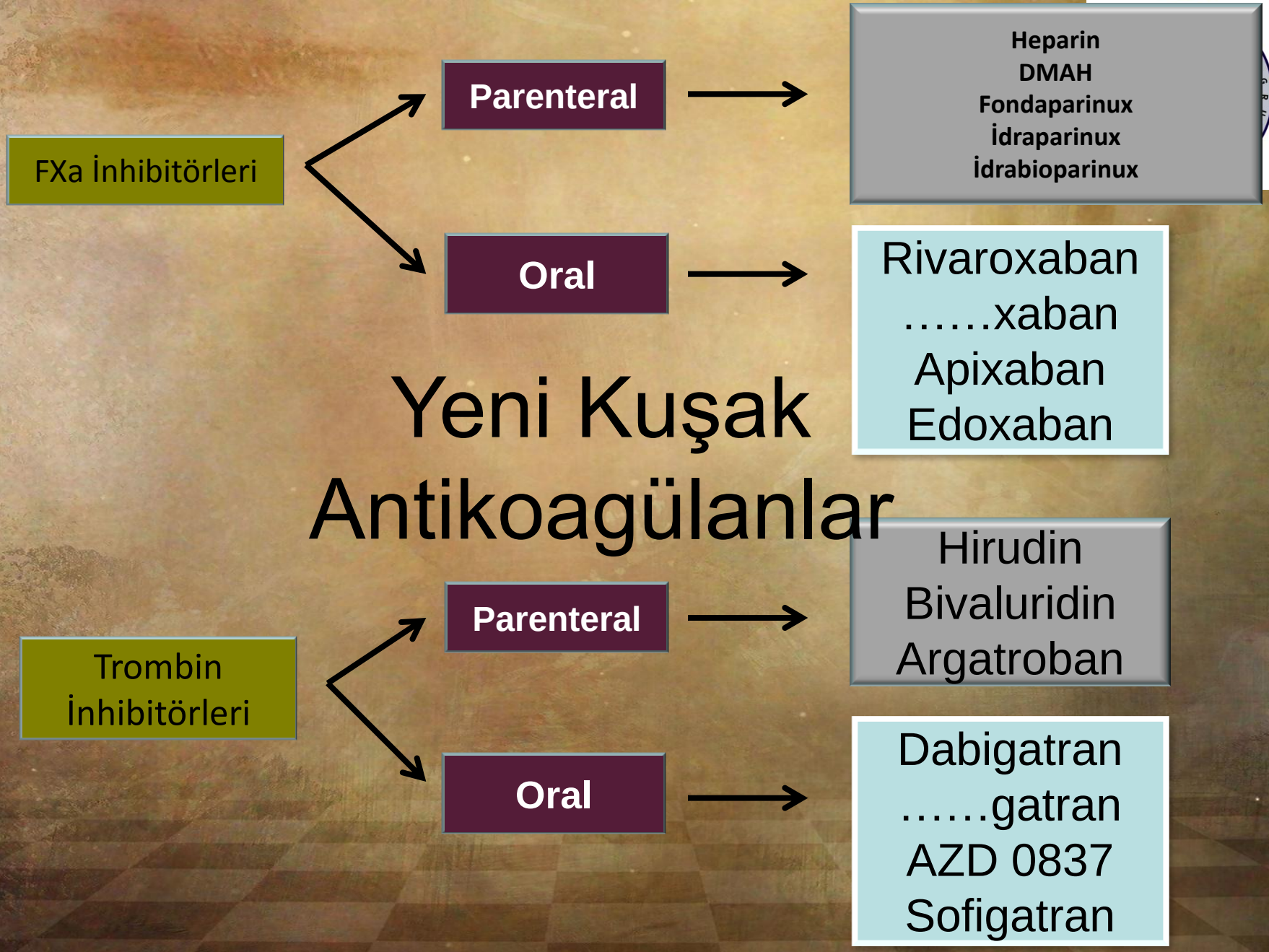
Present studies focused on the *in vitro* testing, the solubility enhancement and the *in vivo* testing of methyl propyl trisulfide (MPTS), a newly identified sulfur donor to treat cyanide (CN) intoxication. To enhance the solubility of the lipophilic MPTS, various FDA approved co-solvents, surfactants and their combinations were applied. The order of MPTS solubility in the given co-solvents was found to be the following: ethanol >> PEG 200 ≈ PEG400 ≈ PEG300 > PG. The maximum solubility of MPTS was found at 90% ethanol of 177.11 ± 12.17 mg/ml. The order of MPTS solubility in different surfactants is Cremophor EL > Cremophor RH40 > polysorbate 80 > sodium deoxycholate > sodium cholate. The maximum solubility of 40.99 mg/ml was achieved with 20% Cremophor EL. A synergistic solubilizing effect encountered with the combination of 20% Cremophor EL + 75% ethanol lead to a 2900-fold increase (compared to water solubility) in solubility. The *in vivo* efficacy using intramuscular administration was determined on a therapeutic mice model and expressed as a ratio of CN LD50 with and without the test antidote(s) (APR). Intramuscular administration was shown to be effective and the therapeutic antidotal protection by MPTS alone and MPTS + thiosulfate (TS) was significantly higher than the present therapy of TS.

sodium thiosulfate in vitro. The fact that DMTS converts cyanide to thiocyanate more efficie
it a promising sulfur donor-type cyanide antidote (scavenger) with reduced enzyme depende
for DMTS versus sodium thiosulfate were measured following intramuscular administration i
ratios (APR = LD_{50} of cyanide with antidote/LD_{50} of cyanide without antidote). A dose of 1D
only slight therapeutic protection (APR = 1.1), whereas the antidotal protection from DMTS
(APR = 3.3). Based on these data, DMTS will be studied further as a promising next-gener

4. Conclusion

The identification of a possible antidote (MPTS) for CN intoxication and its solubilization for the therapeutic antidotal studies using a lethal animal model were addressed in this study. Based on *in vitro* CN to SCN conversion testing of potential sulfur donors it was concluded that MPTS is a potentially effective molecule because its *in vitro* efficacy was superior to that of TS, the SD component in one of the currently approved antidote kits. Following the identification of the SD it was seen that it is a highly lipophilic molecule with low water solubility, thus its solubilization was initiated. Solubility studies revealed that FDA approved excipients, such as co-solvents and surfactants, were able to dissolve MPTS, but a complex system was needed to further increase solubilizing capacity and develop a solvent that can dissolve MPTS at therapeutically relevant concentrations. Further studies showed that co-sol-

Yeni Kuşak Antikoagülanlar



Yeni Kuşak Antikoagülanlar Kanama kontrolü

– Antikoagülanların kesilmesi

– Destek tedavi

(kanama kaynağı kontrolü IV sıvı, ES)

— Erken alımlarda aktif kömür

– Ciddi kanamalarda Nonspesifik prokoagülanlar (PCC ve aFVIIa)

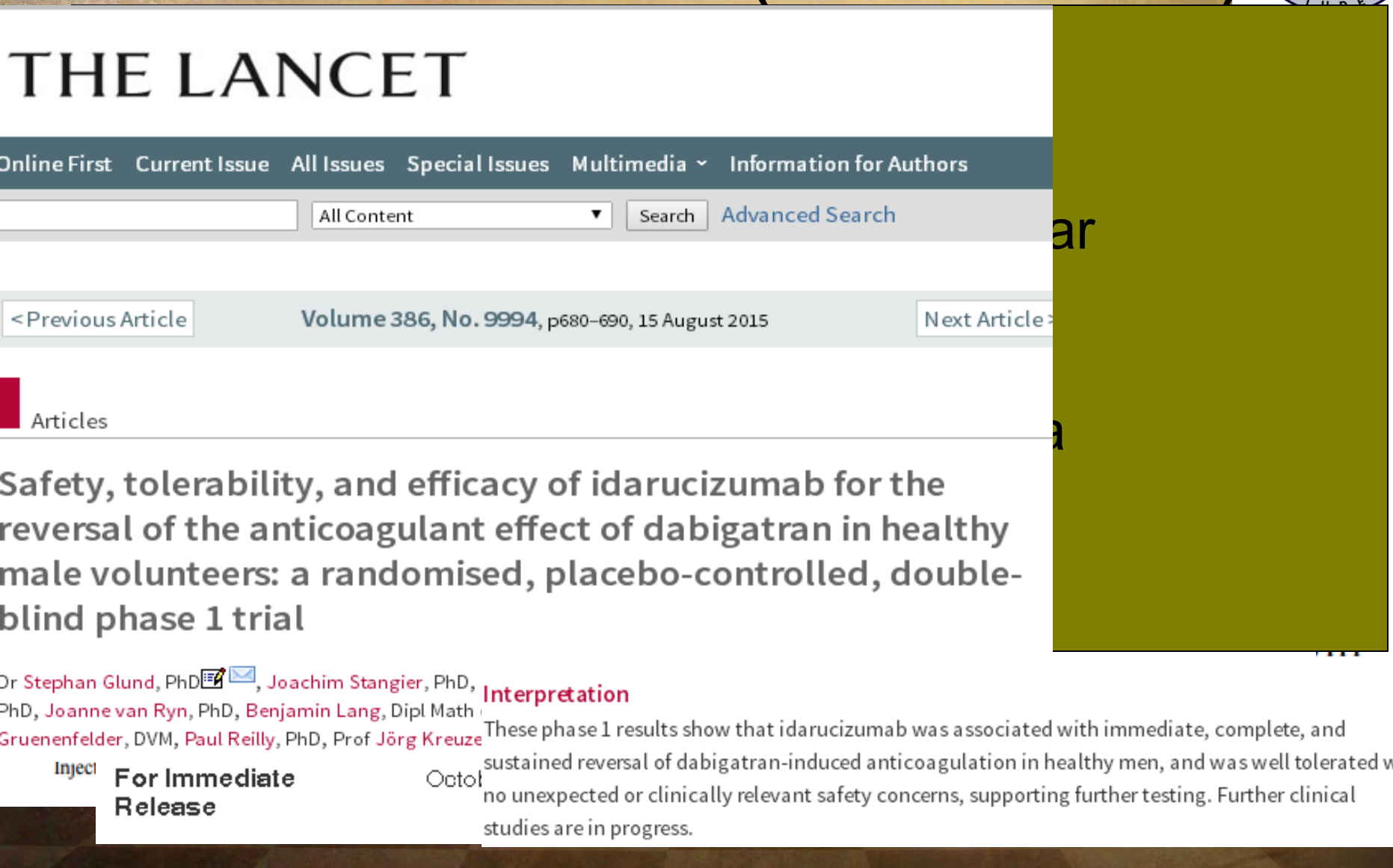
Table 2 Antidotes for NOACs, ongoing and completed clinical trials

Antidote	Study	Study description	Enrollment (number of people)	Results/anticipated completion date	Clinical trial identifier
Perosphere	Phase I, non-randomized	Pharmacokinetic study of single-dose administration of PER977 in healthy subjects	6	August 2014	NCT02205905
	Phase I, RCT	Safety/efficacy of escalating doses of PER977 alone and following one dose of edoxaban	80 Randomized 8:2 to PER977 or placebo	Achieved baseline hemostasis within 10–30 minutes following administration (whole-blood clotting time); effects sustained for 24 hours	NCT01826266
	Phase II, RCT	Safety/efficacy of escalating reversal doses of PER977 following edoxaban. Additionally investigating effects of PER977 on re-anticoagulation with edoxaban and second PER977 reversal	69 Randomized 4:1 to PER977 or placebo	September 2015	NCT02207257
Andexanet alfa	Phase II, RCT	Pharmacokinetics/safety of andexanet alfa in reversing rivaroxaban, apixaban, edoxaban, enoxaparin, and betrixaban	144 Randomized 6:3	November 2013 Preliminary data: Immediate dose-dependent reduction in factor Xa activity that returned to placebo levels by 2 hours following treatment.	NCT01758432
	Phase III, RCT ANNEXA (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors)	ANNEX – A Safety/efficacy of andexanet alfa in reversal of apixaban in healthy 50–75 yo subjects	64	Preliminary data: Immediate reversal of anticoagulation lasting 1–2 hours. Anti-factor Xa activity decreased by 94% and near normalization of ACT	NCT02207725
		ANNEXA – R Safety/efficacy of andexanet alfa in reversal of rivaroxaban in healthy 50–75 yo subjects	79	November 2014	
	Phase III, cohort study	Safety and efficacy of andexanet alfa in achieving hemostasis in patients with major bleeding on direct or indirect factor Xa inhibitors (except lovenox)	270	November 2022	NCT02329327
Idarucizumab	Phase I, RCT	Part 1: Rising dose assessment of idarucizumab in healthy subjects Part 2: Safety and efficacy of idarucizumab in dabigatran reversal in healthy subjects	110 Randomized 3:1 to idarucizumab or placebo 47 Randomized 3:1 to idarucizumab or placebo	Safe and well tolerated. Rapid peak plasma exposure and elimination achieved Immediate, complete, and sustained (72 hours) reversal of dabigatran-induced anticoagulation (dTT, ECT, aPTT, TT) in healthy subjects	NCT01688830
	Phase III, cohort study RE-VERSE AD (A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran)	Safety and efficacy of idarucizumab in dabigatran reversal in patients with serious bleeding (group A) or patients requiring urgent procedure (group B)	Estimated enrollment: 300	July 2017 Interim analysis of 90 patients who received idarucizumab: idarucizumab normalized dTT in ≥93% of patients, ECT in ≥88%, and unbound dabigatran concentration was reduced to minimal levels. Median cessation of bleeding in group A: 11.4 hours. Normal hemostasis achieved in 92% of patients undergoing surgery (92%) in group B	NCT02104947

Abbreviations: ACT, activated clotting time; RE-VERSE AD, Reversal Effects of Idarucizumab on Active Dabigatran; dTT, dilute thrombin time; ECT, ecarin-clotting time; NOACs, novel oral anticoagulants; TT, thrombin time; aPTT, activated partial thromboplastin time; RCT, randomized control trial; yo, years-old.

Hu TY,**Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexanet alfa, andidarucizumab.**Vasc Health Risk Manag.2016

Idarucizumab (Praxbind®)



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Articles

Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial

Dr Stephan Glund, PhD, Joachim Stangier, PhD, PhD, Joanne van Ryn, PhD, Benjamin Lang, Dipl Math Gruenenfelder, DVM, Paul Reilly, PhD, Prof Jörg Kreuze

Inject

For Immediate Release

Octol

Interpretation

These phase 1 results show that idarucizumab was associated with immediate, complete, and sustained reversal of dabigatran-induced anticoagulation in healthy men, and was well tolerated with no unexpected or clinically relevant safety concerns, supporting further testing. Further clinical studies are in progress.

Andexanet alfa (r-Antidote, PRT064445; Portola Pharmaceuticals)

Andexanet alfa (PRT064445) – a factor Xa inhibitor antidote undergoing FDA review

Andexanet at a glance

Mechanism of action	Recombinant and inactivated form of factor Xa Binds factor Xa inhibitors: apixaban, rivaroxaban, and edoxaban
Proposed dose	400 mg IV bolus ±2 hours infusion at 4 mg/min*
Time to effect	2 minutes: 94% decrease in anti fXa activity[‡] Effects of bolus last 1–2 hours
Adverse effects	No known prothrombotic effect – tissue factor pathway inhibitor interaction deserves further investigation
Possible indications	Life-threatening hemorrhage Emergent surgery

Notes: *Dose currently being investigated in Phase III, part 2 trial; ‡data from Crowther et al.[44]

Abbreviation: FDA, Food and Drug Administration; IV, intravenous.

Four separate Phase II randomized, placebo-controlled trials have characterized andexanet alfa's efficacy in a partial reversal of apixaban, rivaroxaban, edoxaban, and enoxaparin. In a small rivaroxaban trial, patients received rivaroxaban 20 mg daily for 6 days followed by escalating doses of andexanet infusion. In those dosed 210 and 420 mg, factor Xa activity was immediately reduced in a dose-dependent manner by 20% and 53%, respectively. Following termination of infusion, factor Xa activity returned to placebo levels by 2 hours following treatment. No serious adverse events were reported.[42]

Currently Phase III ANNEXA trials (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors) are testing the safety and efficacy of andexanet alfa in healthy subjects anticoagulated with apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R). Preliminary data in n=33 (treatment n=24) showed that an andexanet alfa bolus reduced apixaban-mediated anticoagulation immediately. Anti-factor Xa activity decreased by 94% ($P<0.0001$), and near normalization of coagulation (activated clotting time [ACT]) lasted 1–2 hours.[43] In part two of this phase, a 400 mg IV bolus followed by a 2-hour infusion was evaluated for efficacy in reduction of the plasma-free fraction of apixaban and normalization of thrombin generation and sustained effect. Complete results from these Phase III studies are

Crowther M, ANNEXA (TM)-A PART 2: a phase 3 randomized, double-blind, placebo-controlled trial demonstrating sustained reversal of apixaban-induced anticoagulation in older subjects by andexanet ALFA (PRT064445), a universal antidote for factor XA (FXA) inhibitors. J Thromb Haemost.2015

Ciraparantag Aripazine (Perosphere)

Ciraparantag – a universal reversal agent undergoing FDA review

Ciraparantag (PER9	
Mechanism of action	Phase II haemorrhage
Proposed dose	
Time to effect	
Adverse effects	Mild perioral and facial flushing, dysgeusia**
	PT remains elevated
	Does not appear to be sensitive marker for PER977-mediated anticoagulation reversal*
	No prothrombotic effect[1]
Possible indications	Life threatening hemorrhage
	Emergent surgery
	Elective procedures to minimize time off anticoagulation

Notes: *Dose being investigated in Phase II trial; **data from Laulicht et al;[30] [1]data from Ansell et al.[38]

Abbreviations: FDA, Food and Drug Administration; PT, prothrombin time;

Most Recent Events

- **02 Apr 2015** Ciraparantag receives Fast Track designation for Haemorrhage [IV] (In volunteers) in USA
- **05 Nov 2014** Efficacy and adverse events data from a phase I/II trial in Haemorrhage released by Perosphere
- **06 Oct 2014** Aripazine is available for licensing as of 06 Oct 2014. http://www.perosphere.com/

Ciraparantag/PER977: NOACs and heparin antidote

phere, Danbury, CT, USA) is molecule that binds direct Xa ibitors, and unfractionated and LMWH) through non-covalent charge interactions (Table 3). on the exact mechanism of the ion bleeding assays, PER977 coagulants with thromboelas- bleeding. Edoxaban required rsal. In ex vivo human blood studies, PER977 reversed rivaroxaban or apixaban in a dose-dependent fashion, which was quantified by measuring anti-Xa activity.[37] No procoagulant effects were observed in these studies.

In a preliminary study involving 80 healthy patients, PER977 (100–300 mg IV) was administered to subjects 3 hours after receiving edoxaban (60 mg oral). Anticoagulation reversal was monitored with whole-blood clotting time, which correlated with edoxaban plasma concentration. PER977 restored baseline hemostasis within 10–30 minutes and effects were sustained for 24 hours.[38] Phase II trials investigating reversal of edoxaban with escalating doses of PER977 are underway. Plans for Phase III trials with edoxaban have

Laulicht B,. Small molecule antidote for anticoagulants. Circulation. 2012;126:A11395.Ansell JE, Bakhru SH, Laulicht BE,. Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med. 2014;371(22):2141–2142.

İntravenöz Lipid Emulsiyonları

Verapamil Poisoning, the Importance of Intravenous Lipid Therapy: Case Report

Verapamil Zehirlenmesi, İntravenöz Lipid Tedavisinin Önemi: Olgu Sunumu

Verapamil Poisoning, the Importance of Intravenous Lipid Therapy: Case Report

Verapamil Zehirlenmesi, İntravenöz Lipid Tedavisinin Önemi: Olgu Sunumu

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ABSTRACT

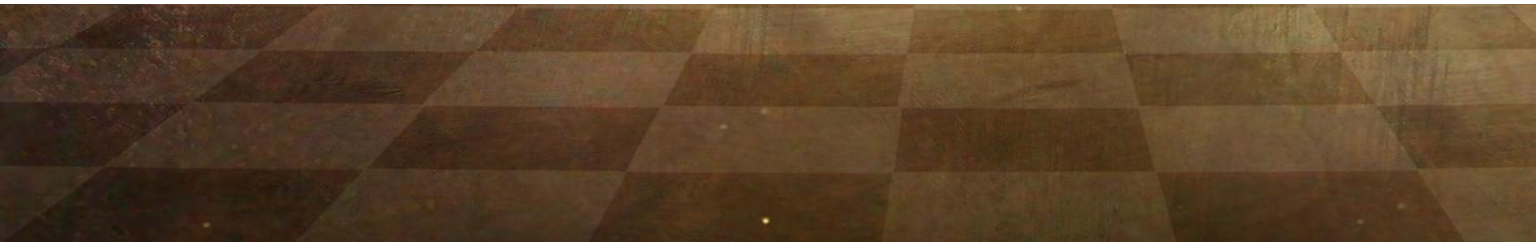
In recent years, intravenous lipid emulsions (ILE) have been used as an effective antidote to lipophilic drug poisonings, especially to local anaesthetic drug intoxication. Massive intentional verapamil overdose is a toxic ingestion that can cause multiorgan failure and currently has no known antidote, which can lead to fatal poisoning. Treatments for calcium channel blocker (CCB) intoxications include decontamination, fluid replacement, vasopressors and glucagon. Here, we present a patient who showed continued hypotension despite aggressive treatment but was successfully resuscitated following intravenous lipid support.

Keywords: Verapamil, intra-venous lipid therapy, intoxication

ÖZET

İntravenöz lipid emülsiyon (İLE) tedavisi son yıllarda başta lokal anestezik ilaç toksisistesi olmak üzere lipofilik olan ilaç zehirlenmelerinde etkin bir antidot olarak kullanılmaktadır. Aşırı doz verapamil alımı, multi organ yetmezliğine yol açabilecek ve kanıtlanmış antidot tedavisi olmayan, ölümcül olabilen zehirlenmelere yol açabilir. Kalsiyum kanal blokörlerine (KKB) bağlı zehirlenmelerin tedavisinde dekontaminasyon, sıvı replasmanı, vasopressör ajanlar, glukagon yer almaktadır. Biz agresif tedaviye rağmen hipotansiyonları devam eden intravenöz lipid desteği sonucu başarı ile resüsite ettiğimiz hastamızı sunuyoruz.

Anahtar Kelimeler: Verapamil, intravenöz lipid



- Bupivakaine bağlı asistolide iv lipit kullanımına dair ilk çalışmalar 90'lı yılların sonu, ratlarda
- 1998 yılında rat modellerinde,
- İnsanlarda ilk kez 2006 yılında Rossenbalt ve ark. Bupivakaine bağlı arrestte başarılı lipid tedavisi

Weinberg GLPretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats Anesthesiology.1998

Etki mekanizması

MEKANİZMA

I. Lipid Sink

II. Biyoenerjitik

III. Ca kanal aktivasyonu

IV. Direkt inotropik etki

•Etkinliğini açıklamakta kullanılan en olası teori

• Uzun zincirli yağ asitlerinin kardiyak miyositlerde voltaj bağımlı kalsiyum kanallarını aktive ettiği bulunmuş (sitozolik Ca artar)

•KKB zehirlenmelerinde diğer ilaçlara oranla daha etkili olabilir?

kompartman

İÇERİK

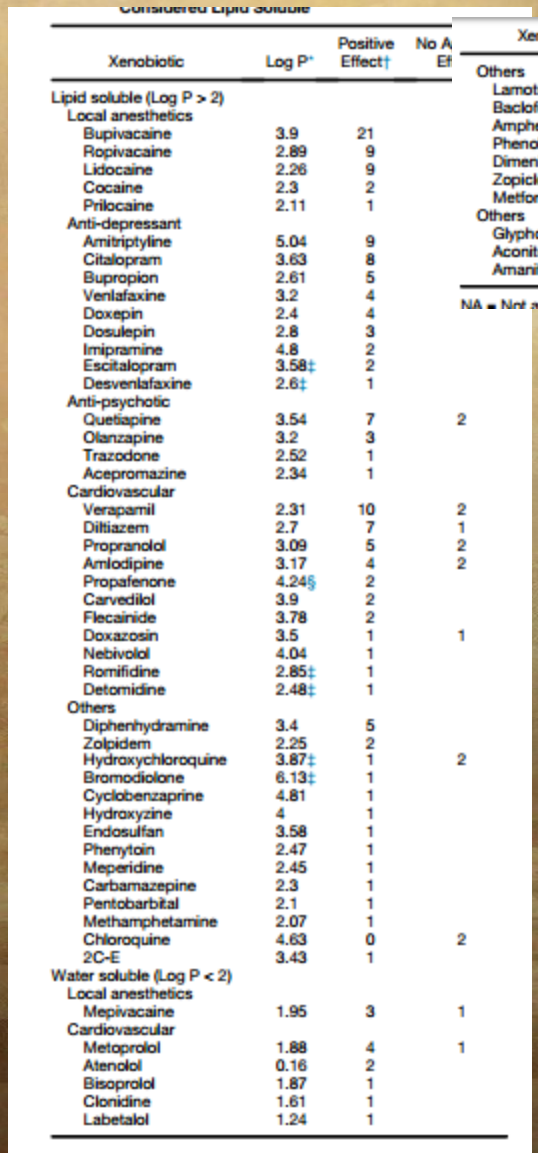
- Trigliserit ve fosfolipit
- Trigliserid ; aspir ya da soya yağı ve uzun zincirli yağ (linoleic, linolenic ,palmitik oleic ,steoric asit) asitlerinden oluşur
- Fosfolipid; yumurta sarısı

- Lokal anestezikler
- Trisiklik antidepresanlar
- Flecainide
- Verapamil,diltizem
- Bupropion,lamotrigin
- Beta blokerler
- Ketiapin ,sertralin,haloperidol,zolpiem
- Kokain

Olgu sunumu

- Literatürde yaklaşık >50 ilaçta bildirilmiş

- Trisiklik antidepressan
- Lamotrijin
- Olanzapin
- Kokain
- Verapamil/Diltiazem
- Haloperidol
- Quetiapin
- Bupropion
- Organofosfatlar (malation paration diazonin)
- Beta blokorler
- Sentetik kanaboidler
- Tramadol
- Endosulfan
- Fenitoin
- Yeni nesil antikoagülanlar



Xenobiotic	Log P*	Positive Effect†	No A Ef
Lipid soluble (Log P > 2)			
Local anesthetics			
Bupivacaine	3.9	21	
Ropivacaine	2.89	9	
Lidocaine	2.26	9	
Cocaine	2.3	2	
Prilocaine	2.11	1	
Anti-depressant			
Amitriptyline	5.04	9	
Citalopram	3.63	8	
Bupropion	2.61	5	
Venlafaxine	3.2	4	
Doxepin	2.4	4	
Dosulepin	2.8	3	
Imipramine	4.8	2	
Escitalopram	3.58‡	2	
Desvenlafaxine	2.6‡	1	
Anti-psychotic			
Quetiapine	3.54	7	2
Olanzapine	3.2	3	
Trazodone	2.52	1	
Acepromazine	2.34	1	
Cardiovascular			
Verapamil	2.31	10	2
Diltiazem	2.7	7	1
Propranolol	3.09	5	2
Amlodipine	3.17	4	2
Propafenone	4.24§	2	
Carvedilol	3.9	2	
Flecainide	3.78	2	
Doxazosin	3.5	1	1
Nebivolol	4.04	1	
Romifidine	2.85‡	1	
Detomidine	2.48‡	1	
Others			
Diphenhydramine	3.4	5	
Zolpidem	2.25	2	
Hydroxychloroquine	3.87‡	1	2
Bromodiolone	6.13‡	1	
Cyclobenzaprine	4.81	1	
Hydroxyzine	4	1	
Endosulfan	3.58	1	
Phenytoin	2.47	1	
Meperidine	2.45	1	
Carbamazepine	2.3	1	
Pentobarbital	2.1	1	
Methamphetamine	2.07	1	
Chloroquine	4.63	0	2
2C-E	3.43	1	
Water soluble (Log P < 2)			
Local anesthetics			
Mepivacaine	1.95	3	1
Cardiovascular			
Metoprolol	1.88	4	1
Atenolol	0.16	2	
Bisoprolol	1.87	1	
Clonidine	1.61	1	
Labetalol	1.24	1	

Xenobiotic	Log P*	Positive Effect†	No Apparent Effect†
Others			
Lamotrigine	1.6	5	1
Baclofen	−0.96	2	
Amphetamine	1.76	1	
Phenobarbital	1.47	1	
Dimenhydrinate	1.1‡	1	
Zopiclone	−0.34	1	
Metformin	−0.31	0	1
Others			
Glyphosate/surfactant	NA	2	
Aconite	NA	1	
Amanita proxima	NA	0	1

NA = Not available

- 61 merkezden 48 olgu
- Lokal anesteziklere bağlı 10 olgu
- Diğer ilaçlarla 38 olgu
- 30 bilinç bozukluğu
- 8 kardiyovasküler kollaps (3 ölüm)
- İLE sonrası GKS ve Kan Basıncı'nda anlamlı değişiklik

J Med Toxicol. 2014 Jan. LIPAEMIC Report: Results of Clinical Use of Intravenous Lipid Emulsion in Drug Toxicity Reported to an Online Lipid Registry.

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http://dx.doi.org/10.1016/j.jemer

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Clinical Review

CrossMark

INTRAVENOUS LIPID EMULSION IN THE
A SYSTEMATIC REVIEW OF RE

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Denver, CO 80204

94 articles included in final analysis

CONCLUSIONS

Since the initial successful report for use in acute bupivacaine-induced cardiac arrest in 2006, intravenous lipid emulsion has been broadly applied for neurologic and cardiac toxic medications. The predominant theory of the lipid sink phenomenon makes this therapy potentially applicable for a wide variety of lipid-soluble xenobiotic-induced toxicities, including local anesthetics, non–dihydropyridine calcium channel blockers, and tricyclic antidepressants. However, the exact mechanism of action has not yet been elucidated and reports of successful resuscitation using lipid emulsion have broadened to include water-soluble xenobiotics, such as β-blockers and lamotrigine. Unfortunately, the lack of high-quality controlled human studies and substantial publication bias toward positive results precludes lipid emulsion therapy as a first-line agent for indications other than local anesthetic systemic toxicity. In the setting of severe hemodynamic compromise caused by a lipid-soluble xenobiotic lipid emulsion therapy may be considered for resuscitation but is not considered to be the standard of care at this time. As such, lipid emulsions may be stocked in emergency departments in close proximity to resuscitation rooms and areas where local nerve blocks are per-

Lipid Solüsyonları

- Lipofundin %10 - %20
- Intralipid %10 - %20
- Lipovenos %10 - %20
- Ivelıp%10 - %20
- Clinoleic %20
- Smoflıpıd %20

İdeal doz

tiate the optimal dose.

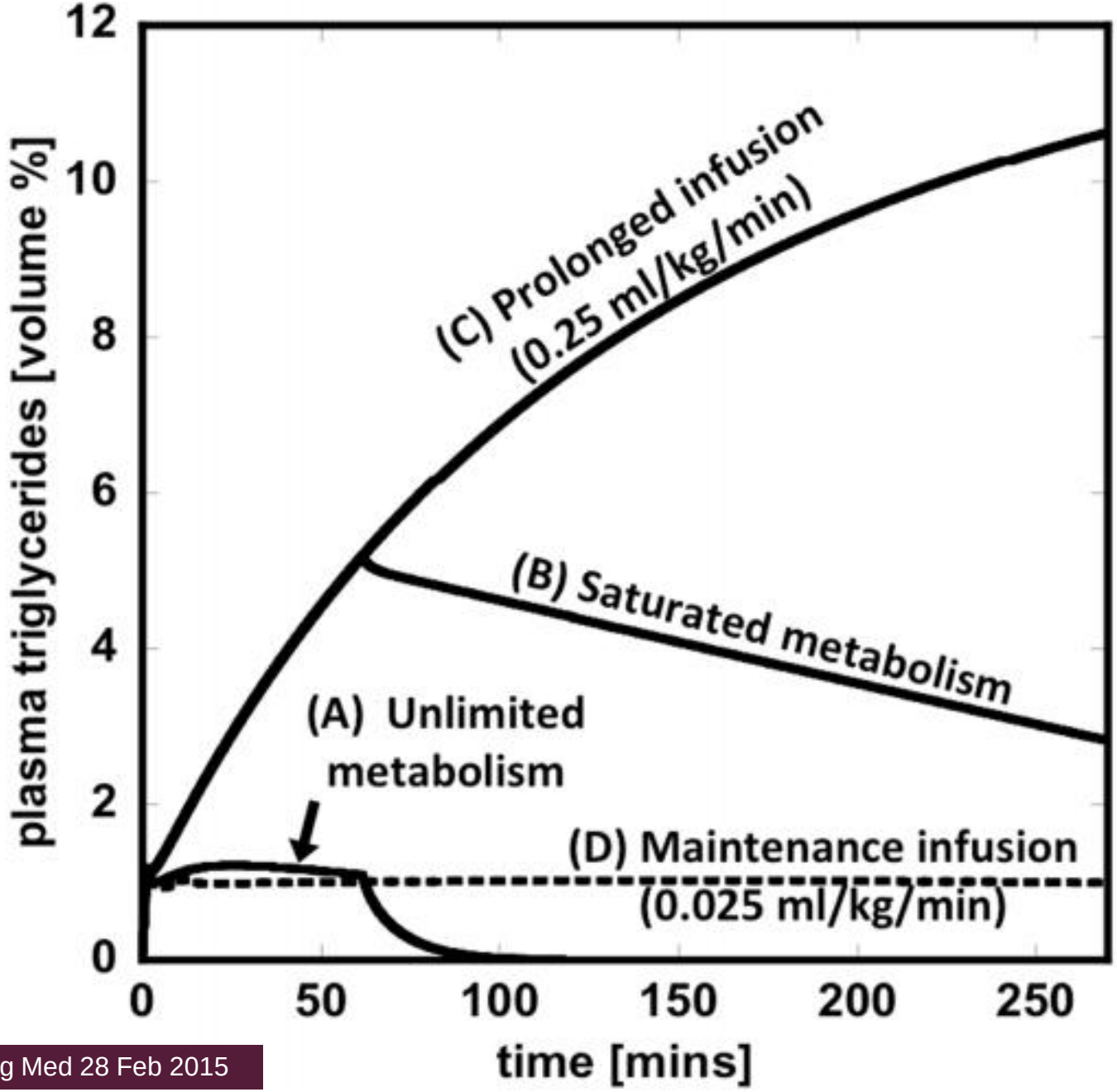
Current recommendation from ASRA for 20% lipid emulsion therapy (123):

1. Bolus 1.5 mL/kg (lean body mass) intravenously over 1 min (note, that dose is in volume, not weight)
   - 100 mL for a 70-kg patient
   - Repeat bolus for persistent cardiovascular collapse
2. Continuous infusion 0.25 mL/kg/min
   - 18 mL/min for a 70-kg patient
   - Can double the infusion rate for persistent hemodynamic instability
   - Continue infusion for at least ten minutes after hemodynamic recovery

- lır

Weinberg lipidrescue.org

Cao D, Intravenous lipid emulsion in the emergency department: a systematic review of recent literature.J Emerg Med. 2015



Ann Emerg Med 28 Feb 2015

Komplikasyonlar

- Laboratuvar bulgularında değişiklikler
- Pankreatit
- Bronkospazm, Anaflaksi (soy bazlı)
- ARDS
- Vasküler komplikasyonlar, Trombofilebit riski ↑
- Kandida enfeksiyon riski↑
- Pulmoner, splenik, serebral v plasental yağ embolileri
- Pulmoner hipertansiyon
- AMS, nöbet
- Kafa içi basınç artışı

- Pancreatitis: Several possible cases of pancreatitis (temporally associated with the administration of intravenous lipids) have been reported.[28,32] The patients did not have adverse effects or require treatment. Pancreatitis associated with lipid infusion is most likely to occur if the patient has received multiple doses or a prolonged infusion of lipid.
- Lung injury: Several cases of lung injury after the use of intravenous lipid as an antidote have been reported.[6,19]

Bartlett D. Intravenous lipids: antidotal therapy for drug overdose and toxic effects of local anesthetics.Crit Care Nurse. 2014.

American Journal of Emergency Medicine 31 (2013) 1536.e1–1536.e2

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journal homepage: www.elsevier.com/locate/ajem

Case Report

Caution with interpreting laboratory results after lipid rescue therapy

- ILEsonrası kan trigliserit↑
- Karaciğer fonksiyon testlerinde yanlış yükseklik
- Dilüsyon/santrifügasyon kullanılabilir

Teşekkürler….