Ufuktaki Antidotlar

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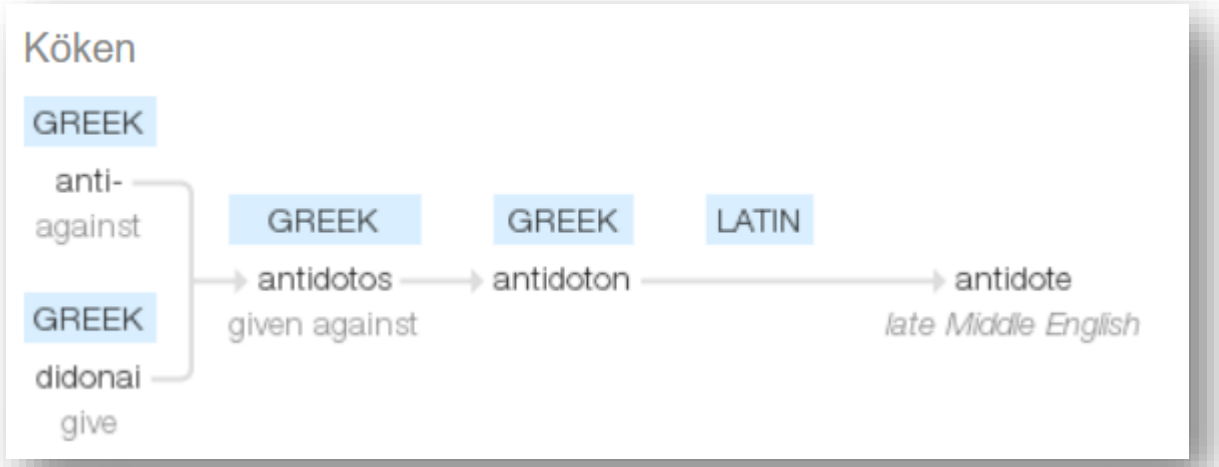
22. Acil Tıp Bahar Sempozyumu 09 - 11 Mart 2018 AYDIN

Antidot Nedir?

- Zehirin toksikokinetik ve toksikodinamiğini değiştirebilen,
- Kullanımı güvenli,
- Zehirlenen kişide dikkate değer yararlı etkileri olan madde
- Halk arasında panzehir, farmakolog ve toksikologlar arasında ise «yetim ilaç»



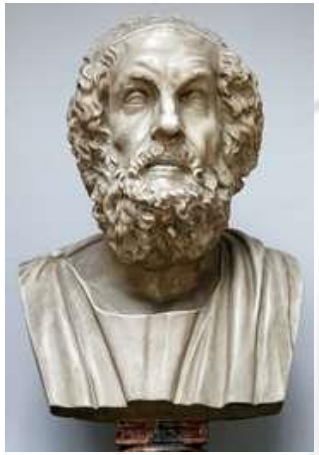
İdeal Antidot Nasıl Olmalı?

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

Antidot İhtiyacı Neden Oluştu?

- Özellikle Roma Döneminde cinayet amaçlı zehirlenme yaygındı. Nero'nun annesi Locustayı İmparator Claudius'u ve üvey kardeşi Brittanicus'u zehirletmek için kiraladı. Nero imparator oldu.
- İlk kez MÖ 81'de Diktatör Sulla suçlulara ceza yaptırımı uyguladı (Lex Cornelia)
- Pontus Kralı VI.Mithradates (MS 132-63) gençliğinde defalarca zehirlenmeye çalışılması ve 36 bileşeni olan mitradatum'u üretmesi.
- Andromachus (M.S. 37-68) mitradatum'u 73 bileşene çıkardı

İlk Antidot



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Clin Neuropharmacol. 1983 Mar;6(1):1-5.

Homer's moly identified as Galanthus nivalis L.: physiologic antidote to stramonium poisoning.

Plaitakis A, Duvoisin RC.

Abstract

The antidotal properties of certain naturally occurring medicinal plants against c
empirically established in ancient times. Homer, in his epic poem, the Odyssey,
against Circe's poisonous drugs. Centrally acting anticholinergic agents are tho
delusional state in Odysseus' crew. We present evidence to support the hypoth
nivalis, which contains galanthamine, a centrally acting anticholinesterase. Thu
may represent the oldest recorded use of an anticholinesterase to reverse centr

PMID: 6342763

[Indexed for MEDLINE]

Adi Kardelen

Bitki

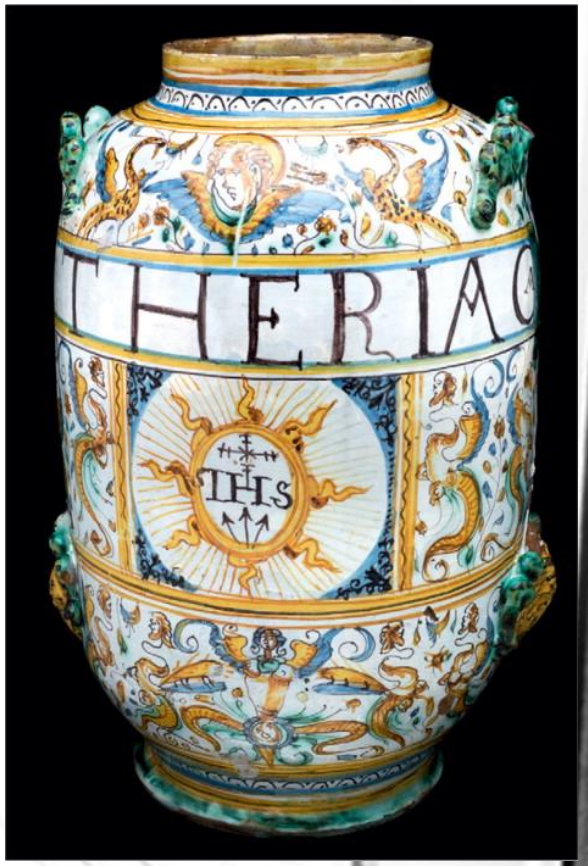
Bilimsel adı: Galanthus nivalis

Üst sınıf: Kardelen

Takson Basamağı: Tür

Tarihte diğer Antidotlar

- Yunan mitolojisinde şifa tanrıçası **Panacea**'nın her hastalığı iyileştiren bir iksire sahip olduğu söylenir.
- İnsanlar her çeşit toksine karşı kişiyi koruyabilen ve **theriac** denen evrensel antidotun peşindedir.
- İlk Theriac formülü, Kos adasında Eskülap tapınağında taş üzerinde kayıtlıdır.
- Terra sigillata adı evrensel bir panzehir ortaya çıktı. Bu çömlek şeklinde,"kutsal mühürlenmiş toprak" olarak da bilinen kırmızı kil Yunan adası olan Lemnos'ta sadece bir tepede bulunabiliyordu.
- Anadolunun antidotu " Mesir Macunu" 41 değişik baharattan oluşur.



Antidotlara Ulaşım

- Antidotlarla ilgili bilgiler, uluslararası organizasyonlarca yayınlanır:
- WHO (World Health Organisation)
- Micromedex
- Uptodate
- Medscape
- Türkiye'de 2001 yılından bu yana sorumlu olan kurum RSHM Başkanlığı Zehir Danışma Merkezi

Son Dönemde Antidotlar

Dantrolene (p. 1001)	Malignant hyperthermia
Deferoxamine mesylate (Desferal) (p. 604)	Iron
Dextrose in water (50% adults;	Hypoglycemia
disodium versenate, $CaNa_2$ EDTA) (p. 1290)	
Ethanol (oral and parenteral dosage forms) (p. 1419)	Methanol, ethylene glycol
Fat emulsion (Intralipid 20% (p. 976)	Cardiac arrest, local anesthetics
Flumazenil (Romazicon) (p. 1072)	Benzodiazepines
Folinic acid (Leucovorin) (p. 783)	Methotrexate, methanol
Fomepizole (Antizole) (p. 1414)	Ethylene glycol, methanol
Glucagon (p. 910)	β-Adrenergic antagonists, CCBs
Glucarpidase (p. 787)	Methotrexate
Hydroxocobalamin (Cyanokit) (p. 1695)	Cyanide
Insulin (p. 893)	β-Adrenergic antagonists, CCBs, hyperglycemia
Iodide, potassium (SSKI) (p. 1775)	Radioactive iodine (I^{131})
Phentolamine (p. 1096)	Cocaine, MAOI interactions, epinephrine, and ergot alkaloids
Physostigmine salicylate (Antilirium) (p. 759)	Anticholinergics
Sodium bicarbonate (p. 520)	Ethylene glycol, methanol, salicylates, cyclic antidepressants, methotrexate, phenobarbital, quinidine, chlorpropamide, type 1 antidysrhythmics, chlorphenoxy herbicides
Sorbitol (p. 114)	Induces catharsis
Starch (p. 1349)	Iodine
Succimer (Chemet) (p. 1284)	Lead, mercury, arsenic
Thiamine hydrochloride (Vitamin B_1.) (p. 1129)	Thiamine deficiency, ethylene glycol, chronic ethanol consumption ("alcoholism")
Vitamin K_1 (Aquamephyton) (p. 876)	Warfarin or rodenticide anticoagulants

Mekanizmaya Göre Antidotlar

Kimyasal Antagonistler

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

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

Mekanizmaya Göre Antidotlar

Fizyolojik Antagonistler

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

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

Mekanizmaya Göre Antidotlar

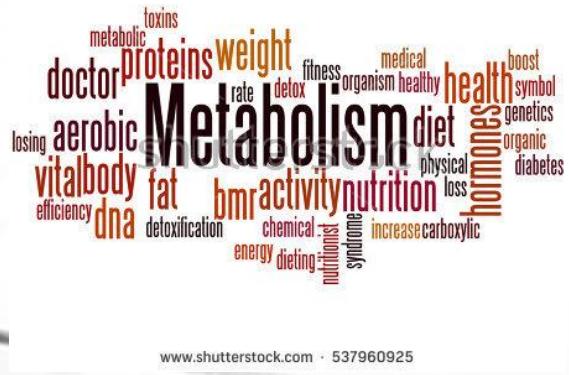
Farmakolojik antagonistler

Zehirlenme etkeninin etkilediği reseptörü bloke ederek antidotal etkinlik yaparlar.

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

Mekanizmaya Göre Antidotlar

Metabolizma düzeyindeki antagonistler

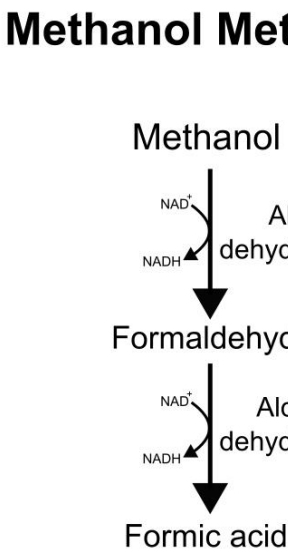


İlaç	Antidot
Warfarin(Coumadin)	K1- vit
CO	Saf Oksijen
Methotreksat	Folinik asit (Leucovorin)
Metil alkol ve etilen glikol	Etanol
Siyanür	Na-tiyosülfat
Asetaminofen	NAC
Organofosfatlar	PAM, Obidoksim
Methemoglobinemi	Metilen mavisi

Güncel Antidotlar

- Fomepizol
- Lökovorin
- İdarucizumab
- Andexanet alfa
- Aripazine
- Zitramin
- Silibinin
- İntravenöz Lipid
- Oksimler, $MgSO_4$, Antioksidanlar
- Nitrokobinamid

Güncel Antidotlar - Fomepizol



Methanol & Ethylene Glycol Poisoning

Load 15 mg/kg IV infusion over 30 min, THEN

10 mg/kg IV q12hr for 4 doses, THEN increase to 15 mg/kg q12hr

Maintain serum level of 8.6-24.6 mg/L

Treat until ethylene glycol or methanol levels are <20 mg/dL

Dialysis may also be required

Güncel Antidotlar - Leucovorin

Methotrexate overdose:

- Give 15 mg PO, IM or IV every 6 hours
- For a single methotrexate overdose therapy can be stopped when methotrexate levels are confirmed to be below the threshold for toxicity. It is otherwise continued for at least 3 days or until the serum methotrexate level is <0.05 micro mol/L (as per chronic toxicity).

Methanol poisoning:

- Give 2 mg/kg IV every 6 hours until toxicity has resolved.

Gut. 2018 Feb;67(2):395-396. doi: 10.1136/gutjnl-2017-314138. Epub 2017 Jun 7. No abstract available.
PMID: 28592441
Similar articles

The Antidote Is Finally Here! Idarucizumab, A Specific Reversal Agent for the Anticoagulant Effects of Dabigatran

Praxbind®
idarucizumab
INJECTION 5g

Gün

Dabigatran Reversal

- Humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran (Pradaxa) when reversal of the anticoagulant effects are needed for emergency surgery or urgent procedures, or in the event of life-threatening or uncontrolled bleeding
- 5 g IV, provided as 2 separate vials each containing 2.5 g/50 mL (see Administration)
- Limited data support administration of an additional 5 g

Humans
Other Animals

Clear all

Pradaxa was approved in 2010 to prevent stroke and systemic blood clots in patients with atrial fibrillation and for the treatment and prevention of deep venous thrombosis and pulmonary embolism without a specific reversal agent. Now, Praxbind has been approved specifically for Pradaxa under the FDA's accelerated approval program (http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm), which permits drug approval for serious conditions that is likely to provide a clinical benefit.

PubMed ▾ Andexanet alfa[Title]

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Items: 17

1. **Andexanet alfa** to reverse the anticoagulant activity of factor Xa inhibitors: a review of design, development and potential place in therapy.
Sartori M, Cosmi B.
J Thromb Thrombolysis. 2018 Jan 25. doi: 10.1007/s11239-018-1617-2. [Epub ahead of print] Review.
PMID: 29372400
Similar articles

2. Safety, pharmacokinetics, and reversal of apixaban anticoagulation with **andexanet alfa**.
Siegal D, Lu G, Leeds JM, Karbarz M, Castillo J, Mathur V, Hutchaleelaha A, Sinha U, Kitt M, McClure M, Hollenbach SJ, Curnutte JT, Conley PB, Crowther M.
Blood Adv. 2017 Sep 22;1(21):1827-1838. doi: 10.1182/bloodadvances.2017007112. eCollection 2017 Sep 26.
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Günc ne – PER977

PubMed ▾ ciraparantag[Title]

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Items: 4

1. Single-dose **ciraparantag** safely and completely reverses anticoagulant effects of edoxaban.
   Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso MA, Brown K, Dishy V, Lanz HJ, Mercuri MF, Noveck RJ, Costin JC.
   Thromb Haemost. 2017 Jan 26;117(2):238-245. doi: 10.1160/TH16-03-0224. Epub 2016 Nov 17.
   PMID: 27853809
   Similar articles

2. **Ciraparantag** for enoxaparin reversal: Adding to the evidence.
   Weitz JI, Eikelboom JW.
   Thromb Res. 2016 Oct;146:106-107. doi: 10.1016/j.thromres.2016.08.013. Epub 2016 Aug 13. No abstract available.
   PMID: 27544033
   Similar articles

3. **Ciraparantag** safely and completely reverses the anticoagulant effects of low molecular weight heparin.
   Ansell JE, Laulicht BE, Bakhru SH, Hoffman M, Steiner SS, Costin JC.
   Thromb Res. 2016 Oct;146:113-118. doi: 10.1016/j.thromres.2016.07.008. Epub 2016 Jul 18.
   PMID: 27470323
   Similar articles

4. Reversing anticoagulant effects of novel oral anticoagulants: role of **ciraparantag**, andexanet alfa, and idarucizumab.
   Hu TY, Vaidya VR, Asirvatham SJ.
   Vasc Health Risk Manag. 2016 Feb 17;12:35-44. doi: 10.2147/VHRM.S89130. eCollection 2016. Review.
   PMID: 26937198 Free PMC Article
   Similar articles

Ciraparantag (PER97

Mechanism of action

Proposed dose

Time to effect

Adverse effects

Possible indications

xanet alfa	Ciraparantag
ıant factor Xa ariant	Synthetic small molecule
a inhibitors	UFH, LMWH, NOACs (not warfarin)
s with fact r inhibitor nding	Noncovalent hydrogen bond (exact mechanism unclear)
mL sterile vater	None
V bolus pl s infusion*	Single 100 mg IV dose (dose under investigation)
t approved	Not yet approved

d on which FX inhibitor was taken,

Pozoloji – K vitamini antagonist tedavisi sırasında oluşan kanama ve kanamanın perioperatif profilaksisinde

Hedef INR: ≤ 2.1 Minör (acil) cerrahi ya da VKA doz aşımı

Başlangıç INR / Vücut Ağırlığı	7.5	5.9	4.8	4.2	3.6	3.3	3.0	2.8	2.6	2.5	2.3	2.2
50 kg	40	40	40	30	30	30	20	20	X	X	X	X
60 kg	50	50	40	40	30	30	30	20	X	X	X	X
70 kg	60	50	50	50	40	40	30	30	X	X	X	X
80 kg	60	60	60	50	50	40	40	30	X	X	X	X
90 kg	60	60	60	60	50	50	40	30	X	X	X	X
100 kg	60	60	60	60	60	50	40	40	X	X	X	X

Hedef INR < 2.1'in altı

- ✓ Küçük acil cerrahi girişimler (anjiografi veya sınırlı cerrahi girişim)
- ✓ Minör kanamalarda (epistaxis ve Hematüri)

Hedef INR < 1,5'in altı

- ✓Majör kanamalar (sindirim ve santral sistemi)
- ✓Acil cerrahi girişimler

Hedef INR: ≤ 1.5 Majör ve yaşamı tehdit eden kanamalar / cerrahi

Başlangıç INR / Vücut Ağırlığı	7.5	5.9	4.8	4.2	3.6	3.3	3.0	2.8	2.6	2.5	2.3	2.2
50 kg	60	60	60	50	50	50	40	40	30	30	30	30
60 kg	80	70	70	60	60	60	50	50	40	40	40	30
70 kg	90	80	80	70	70	70	60	60	50	40	40	40
80 kg	100	100	90	90	90	80	80	70	60	50	50	40
90 kg	100	100	100	90	90	90	80	80	70	60	50	40
100 kg	100	100	100	100	100	90	90	80	70	70	60	50

centurion

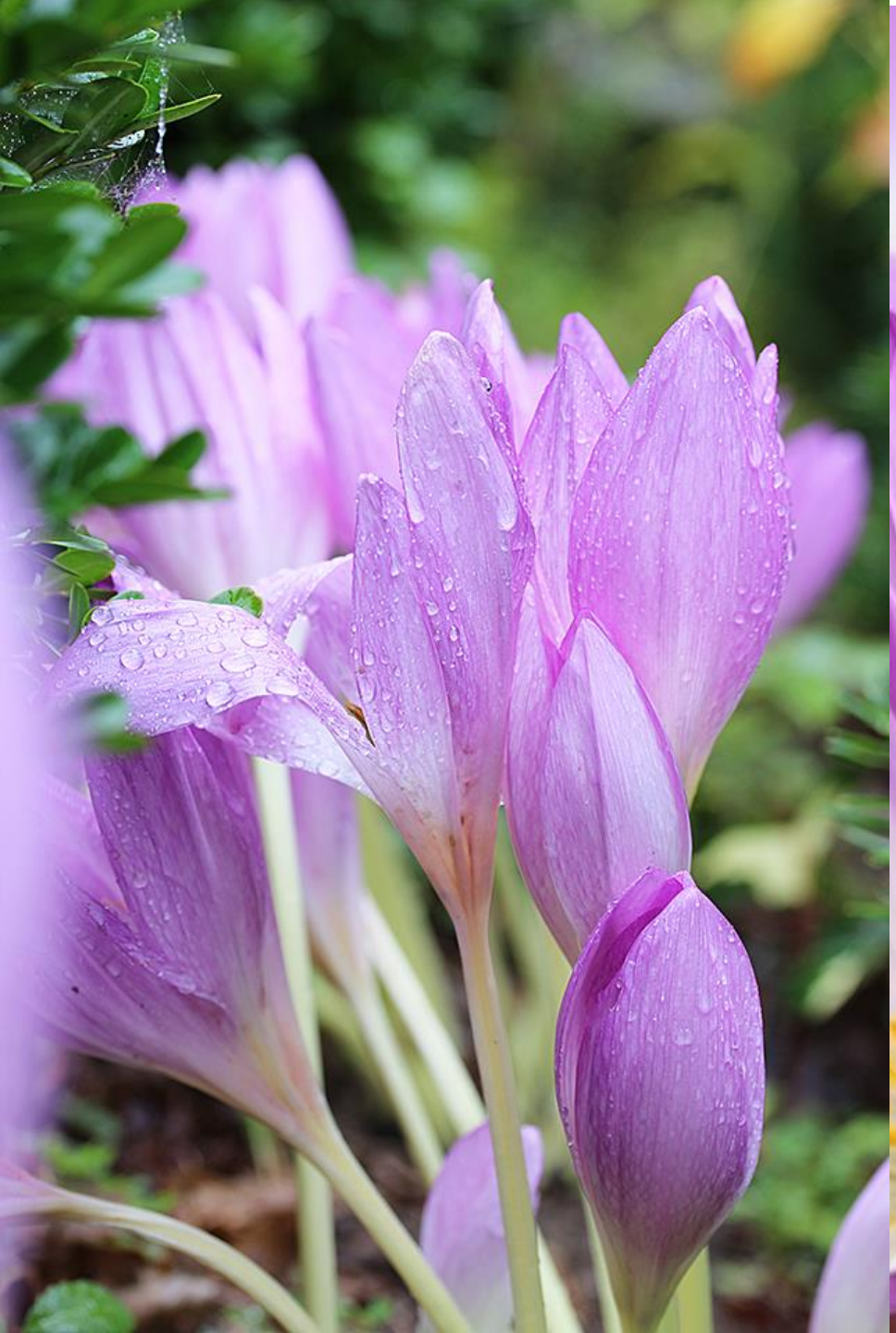
1000 unit range for use with 40 mL vial of Sterile Water for Injection, USP

Cofact®

faktör II, VII, IX, X 10 ve 20 mL

ANTICOAGULANT	TREATMENT	COMMENTS
Antiplatelets (e.g., aspirin, plavix)	Platelets	May need to repeat; consider desmopressin acetate (Deamino-Delta-D-Arginine Vasopressin)
Coumadin (warfarin)	FFP, Vitamin K, prothrombin complex concentrate (Kcentra), Factor VIIa	Normalize INR; avoid fluid overload in elderly patients and patients who sustained cardiac injury
Heparin	Protamine sulfate	Monitor PTT
Low molecular weight heparin, e.g., Lovenox (enoxaparin)	Protamine sulfate	N/A
Direct thrombin inhibitors dabigatran etexilate (Pradaxa)	idarucizumab (Praxbind)	May benefit from prothrombin complex concentrate (e.g., Kcentra)
Xarelto (rivaroxaban)	N/A	May benefit from prothrombin complex concentrate (e.g., Kcentra)

FFP: Fresh frozen plasma; INR: International Normalized Ratio; PTT: Partial thromboplastin time.



Güncel Antidotlar - Zitramin

ISSN 1607-6729, Doklady Biochemistry and Biophysics, 2013, Vol. 451, pp. 215–216. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © M.G. Voronkov, G.G. Yushkov, A.V. Mashanov, A.Yu. Fedorin, M.M. Rasulov, V.V. Benemansky, G.A. Kuznetsova, 2013, published in Doklady Akademii

The trend of changes in the level of ALP activity in blood serum was similar to that observed in the liver homogenate. However, on the third day, these data have lost their informativeness. This phenomenon is characteristic of both chronic and acute ethanol intoxication [2].

In group 2, the activity of serum ALT increased during the entire period of observation (Fig. 4), which is consistent with the published data [3].

The protective effect of THZA was associated with the activity of ADH, in which zinc is present in the active site. Apparently, in experimental animals, THZA is metabolized to yield several active compounds, including ethanolamine, which also inhibits ADH [4]. Thus, it prevents the penetration of C_2H_5OH into cells and exerts an additional antinarcotic effect, contributing to a more rapid elimination of unchanged ethanol [5]. The results of our study confirmed the inhibitory effect of THZA on the activity of ADH in group 3 animals under conditions of acute ethanol intoxication. This disturbs the processes of renewal of the structural and receptor components of hepatocytes and impairs the control over the processes of cell division in animals.

Thus, THZA intensively protects the metabolic processes in animals in ethanol intoxication and reduces the adverse effect of the latter on the liver.

atrane (THZA, zitramin).

nificantly lower than under the effect of ethanol alone.

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2. Zhuravleva, L.V. and Kolesnik, N.T., *Vrach. Delo*, 1986, no. 10, pp. 72–74.
3. Khazanov, A.I., *Lab. Delo*, 1987, no. 10, pp. 736–738.
4. Ostrovskii, S.Yu. and Artsukevich, I.M., *Biokhimiya*, 1989, vol. 54, no. 11, pp. 1888–1893.
5. Ostrovskii, S.Yu., Gorenshtein, B.I., and Bykov, I.L., *Vopr. Med. Khim.*, 1990, vol. 36, no. 6, pp. 63–66.

Translated by M. Batrukova

G

Amanit
mantar
zehirler
karaciğ
tedavis
Paraset
ilaç ve
bağlı ze
karaciğ
önlenm

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41. **Silibinin** Capsules improves high fat diet-induced nonalcoholic fatty liver disease in hamsters through modifying hepatic de novo lipogenesis and fatty acid oxidation.
Cui CX, Deng JN, Yan L, Liu YY, Fan JY, Mu HN, Sun HY, Wang YH, Han JY.
J Ethnopharmacol. 2017 Aug 17;208:24-35. doi: 10.1016/j.jep.2017.06.030. Epub 2017 Jun 23.
PMID: 28648927
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42. Phosphate-Linked **Silibinin** Dimers (PLSd): New Promising Modified Metabolites.
Romanucci V, Gravante R, Cimafonte M, Marino CD, Mailhot G, Brigante M, Zarrelli A, Fabio GD.
Molecules. 2017 Aug 11;22(8). pii: E1323. doi: 10.3390/molecules22081323.
PMID: 28800072 Free Article
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43. Skin Delivery of EGCG and **Silibinin**: Potential of Peptide Dendrimers for Enhanced Skin Permeation and Deposition.
Shetty PK, Manikkath J, Tupally K, Kokil G, Hegde AR, Raut SY, Parekh HS, Mutalik S.
AAPS PharmSciTech. 2017 Aug;18(6):2346-2357. doi: 10.1208/s12249-017-0718-0. Epub 2017 Jan 25.
PMID: 28124212
Similar articles

44. Evaluation of ameliorative ability of **Silibinin** against zidovudine and isoniazid-induced hepatotoxicity and hyperlipidaemia in rats: Role of **Silibinin** in Phase I and II drug metabolism.
Ramanathan R, Sivanesan K.
Chem Biol Interact. 2017 Aug 1;273:142-153. doi: 10.1016/j.cbi.2017.06.008. Epub 2017 Jun 13.
PMID: 28619387
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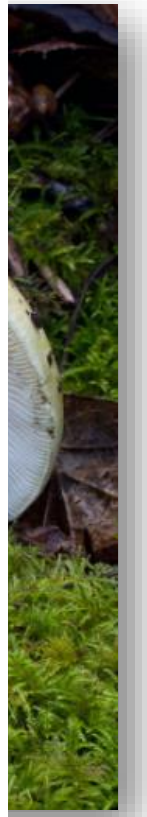

VOLUME 41, NO. 5 — SEPTEMBER-OCTOBER, 1962

ALLEVIATION OF BARBITURATE DEPRESSION

- 1.5 ml/kg Intralipid (20%) over 5-15 minutes, followed by 0.25 ml/kg/min for 30-60 min
  - Simplified: 1.5 ml/kg over 10 min followed by 15 ml/kg over 1 hour
- Dose can be repeated in 4-6 hours if clinical signs of toxicity return

the duration of anesthesia produced by thiopental. This barbiturate is concentrated in fat depots during a period of anesthesia.[1] Experimental lean dogs (presumably less fat) have been found to remain anesthetized longer than heavier control dogs after administration of thiopental.[2] Hermann and Wood[3] found that a 5 per cent decrease in the body fat of the rat resulted in a 100 per cent increase in the length of thiopental an-

METHODS

The duration of anesthesia was recorded as the time elapsed between onset of anesthesia (assumption of side position) and sufficient recovery for the rat to be able to stand.[5] During the entire course of the anesthesia the animals were stimulated mildly every 15 seconds by manually rolling them over and back to the side position.

RESULTS

1. *Effect of Cottonseed Oil Emulsion on the Duration of Anesthesia in the Rat*

thesia for the two groups of rats to be significantly different ($p<0.009$).

CONCLUSIONS

Vegetable fat emulsions infused into the blood stream shorten the duration of thiopental anesthesia in adult male rats.

Güncel Antidotlar – Siyanid Antidotları

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

Chan A[1], Crankshaw DL, Monteil A, Patterson SE, Nagasawa HT, Briggs JE, Kozocas JA, Mahon SB, Brenner M, Pilz RB, Bigby TD, Boss GR.

Author information

Abstract

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.

Güncel Antidotlar – Siyanid Antidotları

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

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

⊕ Author information

Abstract

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

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Advances in toxicology and medical treatment of chemical warfare nerve agents.

Moshiri M[1], Darchini-Maragheh E, Balali-Mood M.

Author information

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.

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Oximes for acute organophosphate pesticide poisoning.

Buckley NA[1], Eddleston M, Li Y, Bevan M, Robertson J.

Author information

Abstract

BACKGROUND: Acute organophosphorus pesticide poisoning causes tens of thousands of deaths each year across the developing world. Standard treatment involves administration of intravenous atropine and oxime to reactivate inhibited acetylcholinesterase. The clinical usefulness of oximes, such as pralidoxime and obidoxime, has been challenged over the past 20 years by physicians in many parts of the world.

OBJECTIVES: To quantify the effectiveness and safety of the administration of oximes in acute organophosphorus pesticide-poisoned patients.

SEARCH STRATEGY: We searched both English and Chinese databases: Cochrane Injuries Group Specialised Register, Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE (Ovid SP), EMBASE (Ovid SP), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED), ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) and the Chinese language databases CNKI and WANGFANG. All searches were run in September 2009.

SELECTION CRITERIA: Articles that could possibly be RCTs were retrieved to determine if they were randomised.

DATA COLLECTION AND ANALYSIS: The published methodology of three RCTs was not clear. We contacted the principal authors of these, but did not obtain further information.

MAIN RESULTS: Seven pralidoxime RCTs were found. Three RCTs including 366 patients studied pralidoxime vs placebo and four RCTs including 479 patients compared two or more different doses. These trials found quite disparate results with treatment effects ranging from benefit to harm. However, many studies did not take into account several issues important for outcomes. In particular, baseline characteristics were not balanced, oxime doses varied widely, there were substantial delays to treatment, and the type of organophosphate was not taken into account. Only one RCT compared the World Health Organization (WHO) recommended doses with placebo. This trial showed no clinical benefits and a trend towards harm in all sub-groups, despite clear evidence that these doses reactivated acetylcholinesterase in the blood.

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Study of Effect of Magnesium Sulphate in Management of Acute Organophosphorous Pesticide Poisoning.

Vijayakumar HN[1], Kannan S[1], Tejasvi C[1], Duggappa DR[1], Veeranna Gowda KM[2], Nethra SS[1].

Author information

Abstract

BACKGROUND: Organophosphorus compound poisoning (OPCP) is a major public health problem in developing countries like India. Atropine and oximes remain the main-stay of management. Magnesium sulfate ($MgSO_4$) has shown benefit in the management of OPCP.

AIMS: This study was designed to assess the effect of $MgSO_4$ on outcome in OPCP patients admitted to Intensive Care Unit (ICU).

SETTINGS AND DESIGN: Double-blind prospective randomized clinical trial in an ICU of tertiary care institution.

METHODS: One hundred patients (50 in each group) of OPCP, confirmed by history and syndrome of OPCP with low plasma pseudocholinesterase, aged between 18 and 60 years were studied. Magnesium group (Group M) received 4 g of 20% $MgSO_4$ infusion ove 30 min at admission to ICU, control group (Group C) received normal saline placebo in the same manner. Patients were assessed for the need for intubation, requirement of atropine, duration of mechanical ventilation, duration of ICU stay, and its effect on mortality.

STATISTICAL ANALYSIS: Chi-square test and Fisher's exact test for categorical data, independent sample *t*-test, and paired *t*-test for nominal data.

RESULTS: Demographics and basal serum magnesium levels were comparable. Atropine requirement was higher in Group C (74.82 ± 22.3 mg) compared to Group M (53.11 ± 45.83 mg) ($P < 0.001$). A total of 33 patients in Group C and 23 patients in Group M required intubation, respectively ($P = 0.043$). The mean duration of mechanical ventilation was 4.51 ± 2 days in Group C compared to 4.13 ± 1.6 days in Group I ($P = 0.45$). ICU stay was 5.36 ± 2.018 days in Group C compared to 4.54 ± 1.581 days in Group M ($P = 0.026$). There was no significant difference in mortality between the groups.

CONCLUSION: Four grams of $MgSO_4$ given to OPCP patients within 24 h of admission to ICU, decreases atropine requirement, need for intubation, and ICU stay.

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Table 3 New recommended treatments for organophosphorous nerve agents

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

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Bioscavenger for protection from toxicity of organophosphorus compounds.

Saxena A[1], Sun W, Luo C, Myers TM, Koplovitz I, Lenz DE, Doctor BP.

Author information

Abstract

Current antidotal regimens for organophosphorus compound (OP) poisoning consist of a combination of pretreatment with a spontaneously reactivating AChE inhibitor such as pyridostigmine bromide, and postexposure therapy with anticholinergic drugs such as atropine sulfate and oximes such as 2-PAM chloride (Gray, 1984). Although these antidotal regimens are effective in preventing lethality of animals from OP poisoning, they do not prevent postexposure incapacitation, convulsions, performance deficits, or, in many cases, permanent brain damage (Dunn and Sidell, 1989). These problems stimulated the development of enzyme bioscavengers as a pretreatment to sequester highly toxic OPs before they reach their physiological targets. Several studies over the last two decades have demonstrated that exogenously administered human serum butyrylcholinesterase (Hu BChE) can be used successfully as a safe, efficacious, and single prophylactic treatment to counteract the toxicity of OPs. It also has potential use for first responders (civilians) reacting to terrorist nerve gas release, pesticide overexposure, or succinylcholine-induced apnea. A dose of 200 mg of Hu BChE in humans is envisioned as a prophylactic treatment that can protect from exposure of 2-5 x LD50 of nerve agents (Ashani, 2000).

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Hum Exp Toxicol. 2013 Jan;32(1):45-52. doi: 10.1177/0960327112455070. Epub 2012 Oct 11.

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

Bayir A[1], Kara H, Köylü O, Kocabas R, Ak A.

Author information

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 ($p = 0.00$ [illegible] 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.

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Basic Clin Pharmacol Toxicol. 2016 Aug;119(2):222-7. doi: 10.1111/bcpt.12554. Epub 2016 Feb 5.

N-acetylcysteine in Acute Organophosphorus Pesticide Poisoning: A Randomized, Clinical Trial.

El-Ebiary AA[1], Elsharkawy RE[1], Soliman NA[2], Soliman MA[3], Hashem AA[1].

Author information

Abstract

Organophosphorus poisoning is a major global health problem with hundreds of thousands of deaths each year. Research interest in N-acetylcysteine has grown among increasing evidence of the role of oxidative stress in organophosphorus poisoning. We aimed to assess the safety and efficacy of N-acetylcysteine as an adjuvant treatment in patients with acute organophosphorus poisoning. This was a randomized, controlled, parallel-group trial on 30 patients suffering from acute organophosphorus poisoning, who were admitted to the Poison Control Center of Tanta University Emergency Hospital, Tanta, Egypt, between April and September 2014. Interventions included oral N-acetylcysteine (600 mg three times daily for 3 days) as an added treatment to the conventional measures versus only the conventional treatment. Outcome measures included mortality, total dose of atropine administered, duration of hospitalization and the need for ICU admission and/or mechanical ventilation. A total of 46 patients were screened and 30 were randomized. No significant difference was found between both groups regarding demographic characteristics and the nature or severity of baseline clinical manifestations. No major adverse effects to N-acetylcysteine therapy were reported. Malondialdehyde significantly decreased and reduced glutathione significantly increased only in the NAC-treated patients. The patients on NAC therapy required less atropine doses than those who received only the conventional treatment; however, the length of hospital stay showed no significant difference between both groups. The study concluded that the use of N-acetylcysteine as an added treatment was apparently safe, and it reduced atropine requirements in patients with acute organophosphorus pesticide poisoning.

Güncel Antidotlar – Organofosfat Zehirlenmeleri

Caramiphen edisylate: an optimal antidote against organophosphate poisoning.

Raveh L[1], Eisenkraft A[2], Weissman BA[3].

Author information

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.

Güncel Antidotlar - MEDI2452

THROMBOSIS AND HEMOSTASIS

Structural and functional characterization of a specific antidote for ticagrelor

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Key Points

- In the clinic, all oral antiplatelet medicines have a risk of bleeding complications.
- We present an antidote for ticagrelor that reverses its antiplatelet effect in human platelet-rich plasma and its bleeding effect in mice.

Ticagrelor is a direct-acting reversibly binding $P2Y_{12}$ antagonist and is widely used as an antiplatelet therapy for the prevention of cardiovascular events in acute coronary syndrome patients. However, antiplatelet therapy can be associated with an increased risk of bleeding. Here, we present data on the identification and the in vitro and in vivo pharmacology of an antigen-binding fragment (Fab) antidote for ticagrelor. The Fab has a 20 pM affinity for ticagrelor, which is 100 times stronger than ticagrelor's affinity for its target, $P2Y_{12}$. Despite ticagrelor's structural similarities to adenosine, the Fab is highly specific and does not bind to adenosine, adenosine triphosphate, adenosine 5′-diphosphate, or structurally related drugs. The antidote concentration-dependently neutralized the free fraction of ticagrelor and reversed its antiplatelet activity both in vitro in human platelet-rich plasma and in vivo in mice. Lastly, the antidote proved effective in normalizing ticagrelor-dependent bleeding in a mouse model of acute surgery. This specific antidote for ticagrelor may prove valuable as an agent for patients who require emergency procedures. (*Blood.* 2015;125(22):3484-3490)

Güncel Antidotlar – N-Asetilsistein amid

Toxicol Lett. 2016 Jan 22;241:133-42. doi: 10.1016/j.toxlet.2015.11.008. Epub 2015 Nov 19.

N-acetylcysteine amide, a promising antidote for acetaminophen toxicity.

Khayyat A[1], Tobwala S[1], Hart M[2], Ercal N[3].

Author information

Abstract

Acetaminophen (N-acetyl-p-aminophenol, APAP) is one of the most widely used over the counter antipyretic and analgesic medications. It is safe at therapeutic doses, but its overdose can result in severe hepatotoxicity, a leading cause of drug-induced acute liver failure in the USA. Depletion of glutathione (GSH) is one of the initiating steps in APAP-induced hepatotoxicity; therefore, one strategy for restricting organ damage is to restore GSH levels by using GSH prodrugs. N-acetylcysteine (NAC), a GSH precursor, is the only currently approved antidote for an acetaminophen overdose. Unfortunately, fairly high doses and longer treatment times are required due to its poor bioavailability. In addition, oral and I.V. administration of NAC in a hospital setting are laborious and costly. Therefore, we studied the protective effects of N-acetylcysteine amide (NACA), a novel antioxidant with higher bioavailability, and compared it with NAC in APAP-induced hepatotoxicity in C57BL/6 mice. Our results showed that NACA is better than NAC at a low dose (106mg/kg) in preventing oxidative stress and protecting against APAP-induced damage. NACA significantly increased GSH levels and the GSH/GSSG ratio in the liver to 66.5% and 60.5% of the control, respectively; and it reduced the level of ALT by 30%. However, at the dose used, NAC was not effective in combating the oxidative stress induced by APAP. Thus, NACA appears to be better than NAC in reducing the oxidative stress induced by APAP. It would be of great value in the health care field to develop drugs like NACA as more effective and safer options for the prevention and therapeutic intervention in APAP-induced toxicity.

Güncel Antidotlar - AM251

Antidote to cannabinoid intoxication: the CB1 receptor inverse agonist, AM251, reverses hypothermic effects of the CB1 receptor agonist, CB-13, in mice.

Pryce G[1], Baker D[1].

Author information

Abstract

BACKGROUND AND PURPOSE: Cannabis is a recreational drug leading to intoxication, following stimulation of cannabinoid CB_1 receptors. However, more recently, herbs mixed with synthetic cannabinoids sometimes known as 'Spice' and 'Black Mamba' have been increasingly used, and their high CB_1 receptor affinity has led not only to marked intoxication but also life-threatening complications and an increasing number of deaths. Although many studies have indicated that prophylactic treatment with CB_1 receptor antagonists can block cannabimimetic effects in animals and humans, the aim of this study was to determine whether CB_1 receptor antagonism could reverse physical cannabimimetic effects.

EXPERIMENTAL APPROACH: Cannabimimetic effects, measured by the hypothermic response following sedation and hypomotility, were induced by the synthetic CB_1 receptor agonist CB-13 (1-naphthalenyl[4-(pentyloxy)-1-naphthalenyl]methanone) in Biozzi Antibody High mice. The CB_1 receptor antagonist/inverse agonist AM251 (N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide) was administered 20 min after the injection of CB-13 and its effects on the cannabimimetic responses were assessed.

KEY RESULTS: In this study, the CNS-related cannabimimetic effects, as measured by the hypothermic effect, induced by the CB_1 receptor agonist were therapeutically treated and were rapidly reversed by the CB_1 receptor antagonist/inverse agonist. There was also a subjective reversal of visually evident sedation.

CONCLUSIONS AND IMPLICATIONS: Cannabinoid receptor antagonists have been widely used and so may provide an acceptable single-dose antidote to cannabinoid intoxication. This use may save human life, where the life-threatening effects are mediated by cannabinoid receptors and not off-target influences of the synthetic cannabinoids or non-cannabinoids within the recreational drug mixture.

Güncel Antidotlar

The woman physician as antidote to the ills of modern medicine.

Gardner SE[1].

Author information

Abstract

This article, drawing on the work of Edith Stein, reflects on the feminine as
person and personal accompaniment. It presents these feminine aspects,
ethos of modern medicine, as a needed corrective to such an ethos. Final
Sweet.


Teşekkürler...