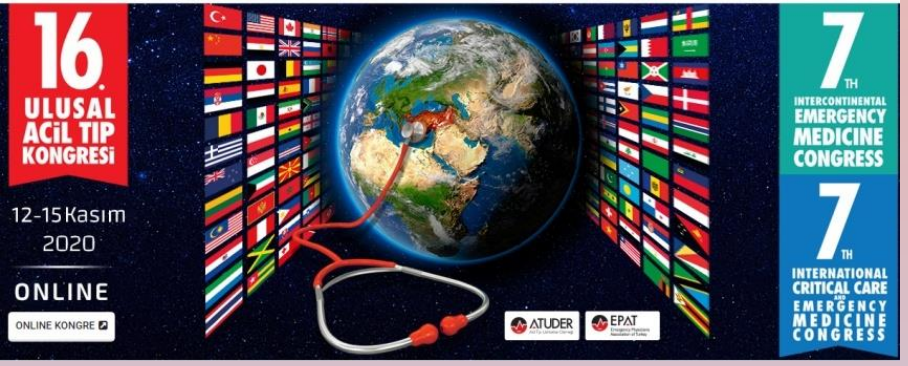


Toksikolojik vakalarda güncel tedavi modelleri

Doç. Dr. Emine Emektar

Keçiören Eğitim ve Araştırma Hastanesi Acil Tıp Kliniği

- Zehirlenme vakaları acil servis başvurularının önemli bir kısmını oluşturmakta
- Bu başvurularda özkıyımlar ve 5 yaş altı çocuklar en büyük paya sahip
- Son dönemlerde yeni tedavi modelleri zehirlenmelerde kullanılmaya başlansa da toksikolojide çok fazla değişen tedavi protokolü yok

Dekontaminasyon

- Kontrollü klinik çalışmalarda, GI dekontaminasyonun "rutin" kullanımının zehirlenme vakalarında morbidite ve mortaliteyi azalttığı gösterilmemiş

- Bununla birlikte, gönüllü insan deneyleri ve klinik çalışmalardan elde edilen kanıtlar, dekontaminasyonun GI kanalındaki toksinlerin emilimini ↓düşündürmekte

Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):140. Epub 2013 Feb 18.
Benson BE, American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists

Gastrik lavaj

- Toksikolojide **rutin** dekontaminasyon yöntemi olarak **önerilmemekte**

- Amerikan ve Avrupa Zehir Merkezleri ve Klinik Toksikologlar Birliği (EAPCCT), intoks hastaların tedavisinde mide lavajının rutin olarak kullanılmaması gerektiğine dair ortak bir bildiri yayınladı (2013)

- Endikasyon
- Son 1 saat içerisinde gelen potansiyel olarak ölümcül miktarda ilaç alımı

Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):140. Epub 2013 Feb 18.
Benson BE, American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists

Aktif karbon

- Aktif kömür, organik materyalin pirolizi ile üretilen aşırı ısıtılmış, yüksek yüzey alanlı, gözenekli partiküllerden yapılan oldukça adsorban bir toz

- Geniş yüzey alanı, kimyasalları birkaç dakika içinde adsorbe eden, gastrointestinal absorpsiyonu ve müteakip toksisiteyi önleyen fonksiyonel gruplar içeren karbon bazlı bir ağ ile kaplı

- Endikasyonları
- AC, toksinler midedeyken büyük olasılıkla fayda sağlar.
- Geleneksel olarak, bu sürenin zehir alımından sonraki bir saat içinde olduğu düşünülmektedir, ancak daha sonra uygulandığında fayda potansiyeli göz ardı edilemez

Çok dozlu aktif kömür

- Bazı durumlarda hastalar, tekrarlanan aktif kömür uygulamasından fayda görebilir

- Üç farklı mekanizma ile etki ettiği düşünülmekte

●Enterohepatik resirkülasyonun kesilmesi

●Vücuttan bağırsak lümenine transluminal difüzyonun kolaylaştırılması ("bağırsak diyalizi") ve ardından ekskresyon

●Uzatılmış veya gecikmiş salimli formülasyonların azaltılmış emilimi

Endikasyonlar - aşağıdaki ilaçların yaşamı tehdit eden yutulmasında yardımcı olabilir , ancak kanıtlar sınırlıdır ve toksikologlar arasındaki görüş birliği yok

- Karbamazepin
- Dapson
- Fenobarbital
- Kinin
- Teofilin
- Asetilsalisilik asit (aspirin)
- Fenitoin

Parasetamol

- Gelişmiş ülkelerde akut KC yetm'nin en sık nedeni
- Çoğu suisit amaçlı, ancak kazara alımlar çocuklarda sık ve supra terapatik overuse !!!
- Yaklaşık 40 yıldır 3 setlik IV NAC infuzyonu uygulanmakta
- Son dönemde alerjik reaksiyonlar ve GI yan etkileri azaltmak için 2 set

3 doz tedavi rejimi
150 mg/kg 1 saatte
50 mg/kg 4 saatte
100 mg/kg 16 saatte

2 doz tedavi rejimi
200 mg/kg 4 saatte
100 mg/kg 16 saatte

EClinicalMedicine 20 (2020) 100288

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study)

Anselm Wong[a,b,c,*], Geoff Isbister[d,e], Richard McNulty[f,g], Katherine Isoardi[h,i], Keith Harris[j,k], Angela Chiew[l,m], Shaun Greene[a,b,n,o], Naren Gunja[g,p,q], Nicholas Buckley[r,s], Colin Page[j,k],

Son dönemde alerjik reaksiyonlar ve GI yan etkileri azaltmak için 2 set infüzyon önerilmekte

Research in Context

Evidence before this study

Paracetamol overdose is the most common pharmaceutical poisoning worldwide and can lead to liver injury or acute liver failure. For the last 40 years, a 3 bag intravenous acetylcysteine regimen has been used to treat paracetamol overdose worldwide. However, adverse reactions to acetylcysteine are common and the infusion regimen is complex. Acetylcysteine regimens that have given an initial loading dose over a longer period have shown to decrease these adverse reactions. Specific to this paper, a 2 bag 20 h acetylcysteine regimen has shown to decrease the number of infusion changes and adverse reactions. However, the efficacy of this regimen to prevent liver injury has not been studied.

Added Value of this study

We present evidence from a multi-centre observational study including nine treatment centres. This study shows that a 2 bag intravenous acetylcysteine regimen is as efficacious compared to the traditional 3 bag regimen to treat paracetamol overdose. The study also confirms that a 2 bag regimen reduced the incidence of non-allergic anaphylactic reactions caused by acetylcysteine in a large cohort.

Implications of all the available evidence

The incidence of paracetamol overdose is increasing in many countries and new treatment regimens are needed to simplify treatment and decrease adverse reactions to acetylcysteine. To our knowledge, this is the first large multi-centre study describing the efficacy and safety of the 2 bag 20 h intravenous acetylcysteine regimen to treat paracetamol overdose. This research will have implications of changing national and international treatment guidelines for the management of paracetamol overdose.

ABSTRACT

Background: Previous studies of paracetamol overdose treatment show that a 2-bag, 20-h intravenous (IV) acetylcysteine regimen decreased the incidence of non-allergic anaphylactic reactions compared to the 3-bag, 21 h IV regimen, but have not examined efficacy of the 20-h 2 bag regimen.

Methods: This was a multi-centre observational study of paracetamol overdose presentations treated with a 2-bag IV acetylcysteine regimen (200 mg/kg over 4 h, 100 mg/kg over 16 h) compared to a 3-bag regimen, performed from 2009 to 2019. Patients were referred from the emergency department to the inpatient toxicology units for continued management. For the primary non-inferiority analysis: subjects had single, acute ingestions, a serum paracetamol-concentration performed 4 to 8-h post-ingestion. The primary outcome was development of acute liver injury (ALI), defined as peak ALT>150 U/L; and > double admission baseline ALT (for presentations within 24 h post-overdose). Secondary outcomes included adverse reactions to acetylcysteine (cutaneous and systemic).

Finding: Out of 6419 paracetamol overdoses, 2763 received acetylcysteine. For the primary analysis, 1003 received the 2-bag and 783 the 3-bag acetylcysteine regimen. When presentation bloods were performed 4 to 8-h post-overdose, 21 (3.1%) developed ALI with the 2-bag regimen vs 16 (2.9%) with the 3-bag regimen (Difference: 0.2%, 95%CI:-1.6 to 2.2). The incidence of hepatotoxicity was: 1.2% ($n = 8$) with the two-bag regimen and 1.6% ($n = 9$) with the three-bag regimen (Difference -0.4%, 95%CI -1.75, 0.91). When presentation bloods were performed 8 to 24-h post-overdose, 70 (21%) developed ALI with the 2-bag regimen vs 46 (23%) with the 3-bag regimen (Difference: -2%, 95%CI -9.12 to 5.36). There were significantly less cutaneous and systemic non-allergic anaphylactic reactions recorded after treatment with the two-bag than the three-bag regimen (1.3% [$n = 17$] and 7.1% [$n = 65$], Difference: -5.8%, 95%CI -7.6 to -4.0, $p < 0.0001$), respectively.

Interpretation: A two-bag intravenous acetylcysteine regimen was found to be non-inferior to the three-bag regimen with regards to efficacy in preventing acute liver injury for early presentations of paracetamol

Table 2. Comparison of the incidence of adverse events between patients presenting with paracetamol overdose who received IV NAC two-bag or three-bag regimens.

No. of subjects (%)	Two-bag regimen $n = 493$	Three-bag regimen $n = 274$	Inference p or CI[a]	All $N = 767$
NAARs total	20 (4)	46(17)	<.001	66(9)
Rash/urticaria	12 (2)	38(14)	<.001	50(7)
Hypotension/edema/respiratory	3 (0.6)	10(4)	.003	13(2)
GI reactions	0	3(1)	.045	3(0.4)
Hepatotoxicity	20 (4)	11(4)	.029, .030[a]	31(4)
Median length of stay (days)	1	2	<.001	1
Treatment delays	27 (5)	33(12)	.002	60(8)
Medication errors	8 (2)	1(0.4)	.169	9(1)

NAARs: non-allergic anaphylactic reaction.
[a]95% CI.

Clinical Research

Fewer adverse effects associated with a modified two-bag intravenous acetylcysteine protocol compared to traditional three-bag regimen in paracetamol overdose

Lars E. Schmidt, Ditlev N. Rasmussen, Tonny S. Petersen, Ines M. Macias-Perez, Leo Pavliv, Byron Kaelin, ...show all

Pages 1128-1134 | Received 23 Feb 2018, Accepted 23 Apr 2018, Published online: 24 May 2018

Journal
Clinical Toxicology ›
Volume 56, 2018 - Issue 11

Acetylcysteine for paracetamol poisoning

Therapeutic Guidelines

Abstract

Introduction: Paracetamol is a common agent taken in deliberate self-poisoning and in accidental overdose in adults and children. Paracetamol poisoning is the commonest cause of severe acute liver injury. Since the publication of the previous guidelines in 2015, several studies have changed practice. A working group of experts in the area, with representation from all Poisons Information Centres of Australia and New Zealand, were brought together to produce an updated evidence-based guidance.

Main recommendations (unchanged from previous guidelines):

- The optimal management of most patients with paracetamol overdose is usually straightforward. Patients who present early should be given activated charcoal. Patients at risk of hepatotoxicity should receive intravenous acetylcysteine.
- The paracetamol nomogram is used to assess the need for treatment in acute immediate release paracetamol ingestions with a known time of ingestion.
- Cases that require different management include modified release paracetamol overdoses, large or massive overdoses, accidental liquid ingestion in children, and repeated supratherapeutic ingestions.

Major changes in management in the guidelines:

- The new guidelines recommend a two-bag acetylcysteine infusion regimen (200 mg/kg over 4 h, then 100 mg/kg over 16 h). This has similar efficacy but significantly reduced adverse reactions compared with the previous three-bag regimen.
- Massive paracetamol overdoses that result in high paracetamol concentrations more than double the nomogram line should be managed with an increased dose of acetylcysteine.
- All potentially toxic modified release paracetamol ingestions (≥ 10 g or ≥ 200 mg/kg, whichever is less) should receive a full course of acetylcysteine. Patients ingesting ≥ 30 g or ≥ 500 mg/kg should receive increased doses of acetylcysteine.

- Paracetamol and ALT concentrations for ***ALL*** at >4 hours after ingestion
- 2-bag acetylcysteine regimen (instead of 3)
- 'Low-dose' –standard 20-hour regimen
- 'High-dose' –double dose in 2ndbag

Repeat paracetamol and ALT concentrations for ALL – 2 hours before the end of the 2nd infusion

- Extended therapy for potential hepatotoxicity, until the patient is well & bloods are normalising

Diğer zehirlenmelerde NAC

- NAC, asetaminofen toksisitesi için tedavinin temel taşı
- pnömoni, bronşit, trakeobronşit, kistik fibroz, postoperatif pulmoner komplikasyonlar, vs gibi endikasyonlarda kullanılmakta
- Etiket dışı endikasyonları akut karaciğer yetmezliği, kontrastnefropatisi önlenmesi ve tedavisi
- Son dönemde diğer zehirlenmelerde

- *Amanita phalloides*
- Arsenic
- Paraquat
- Hydrocarbons:benzene carbon tetrachloride, chloroform
- Some Essential oils: clove oil, pennyroyal oil

High-dose insulin euglycaemia therapy (HIET)

- HIET, hemodinamik parametreleri ve mortaliteyi iyileştirmek için düşük kalite de olsa güçlü kanıtlarla desteklenen bazı zehirlenmelerde kullanılan son dönemlerde günlük pratiğimize giren bir antidot

- Miyokardiyal disfonksiyonu olan zehirlenme vakalarında birinci basamak tedavide

- Mekanizma
- Net mekanizma bilinmiyor. Çoğu veri hayvan deneylerinden
- Myokard hclerine glukoz girişini↑
- Direk myokard üzerinde pozitif inotrop etkili
- SVR↓ böylece deprese myokard yeterli CO ve sistemik perfüzyon sağlar

An Overview of Hyperinsulinemic-Euglycemic Therapy in Calcium Channel Blocker and β-blocker Overdose.

Krenz JR[1], Kaakeh Y[1]

Author information

Pharmacotherapy, 04 Oct 2018, 38(11):1130-1142
DOI: 10.1002/phar.2177 PMID: 30141827
Review

Recommended Approach for HIET in CCB and BB Overdose

1. **Indications for Initiation:** Patients who have ingested potentially toxic amounts of BB or CCB medications who are symptomatic and in whom an increase in myocardial function is desired. Symptoms may include decreased HR and/or BP. Symptomatic patients may also experience abnormalities in peripheral vascular resistance or altered mental status. Patients may present with EKG abnormalities such as sinus bradycardia, AV block, or QTc prolongation

2. **Regular Insulin IV Bolus:** Administer 1 unit/kg as a single bolus dose.

3. **Regular Insulin IV infusion:** Initiate infusion at 0.5 to 1 unit/kg/hour. Titrate upward every 10 to 15 minutes to clinical response. Reasonable maximum dose: 10 units/kg/hour.

4. **Maintain Euglycemia:** Administer continuous dextrose infusion concomitantly with regular insulin infusion to maintain BG concentration greater than 100 mg/dL. Immediate dextrose supplementation may not be necessary in severe CCB overdose due to insulin resistance; check initial BG concentration in these patients and hold dextrose if BG $\geq$ 200 mg/dL. Initiate dextrose at 0.5 g/kg/hour. Concentrations of $\geq$ 20% dextrose administered via central line may be preferred to prevent fluid overload.

5. **Efficacy Targets:** No consensus on ideal efficacy targets in published literature. Reasonable to target a systolic BP of $\geq$ 90 mmHg and HR $\geq$ 50 bpm. If present at baseline, abnormalities in mental status and EKG readings should resolve.

6. **Consider Potassium Supplementation:** Administer IV potassium supplementation as needed to maintain serum potassium concentrations at or above 3 mEq/L.

7. **Monitoring Parameters:** Continually monitor vital signs and symptoms of overdose including HR, BP, mean arterial pressure, signs of adequate perfusion, and mental status changes. Monitor BG every 15 to 60 minutes. Monitor serum potassium every hour upon therapy initiation, then every 60 to 120 minutes once stable. Monitor serum electrolytes such as magnesium and phosphorous hourly, then every 4-6 hours once patients are stable. Serial EKG monitoring until patients stabilize may be beneficial for those with abnormalities at initial presentation.

8. **Duration of Therapy:** Reasonable to continue HIET until hemodynamic stability is achieved and patient is stable. Therapy should be slowly tapered off over a period of at least several hours. Continually monitor for worsening BP, HR, or mental status as therapy is discontinued. Consider continuing dextrose for several hours after weaning insulin to avoid hypoglycemia.

Digoksin zehirlenmesi

- Akut digoksin zehirlenmesinin tedavisinin kronik digoksin birikiminden farklı olup, son dönemde digoksin toksisitesi yönetimi için değişen kanıtlar ortaya çıkmıştır (DORA study)
- **Özellikle digoksin immün Fab dozları**

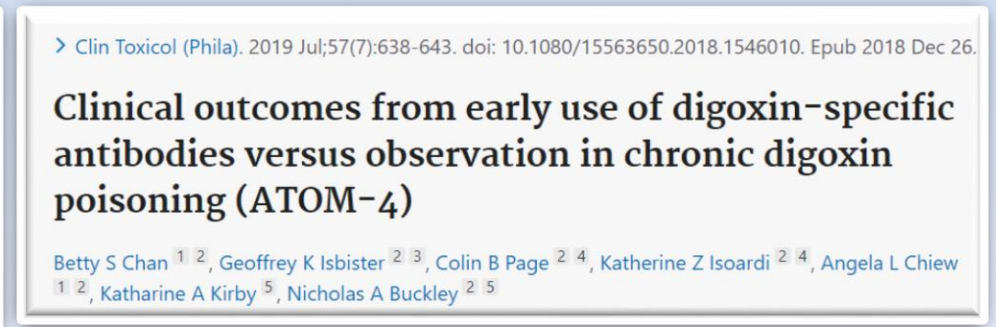
- Daha önce öneriler, digoksin immün Fab dozları, hastanın serum digoksin konsantrasyonuna göre
- Bu genellikle aşırı dozda digoksin immün Fab ile sonuçlanabileceği

- Kronik digoksin birikiminde çoğu hasta digoksin immün Fab ile tedaviye ihtiyaç duymayacağı gösterildi


Observational Study > Clin Toxicol (Phila). 2016 Jul;54(6):488-94.
doi: 10.1080/15563650.2016.1175620. Epub 2016 Apr 27.

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

Betty S Chan [1 2], Geoffrey K Isbister [2 3 4], Margaret O'Leary [3 4], Angela Chiew [1 2], Nicholas A Buckley [2 5]


> Clin Toxicol (Phila). 2019 Jul;57(7):638-643. doi: 10.1080/15563650.2018.1546010. Epub 2018 Dec 26.

Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4)

Betty S Chan [1 2], Geoffrey K Isbister [2 3], Colin B Page [2 4], Katherine Z Isoardi [2 4], Angela L Chiew [1 2], Katharine A Kirby [5], Nicholas A Buckley [2 5]

Acute digoxin poisoning

Klasik

Amount of digoxin ingested is known but concentration is unknown — The number of Fab fragment vials to give the patient with an acute overdose, when only the amount ingested is known, is based upon the total body load:

- Step 1 – Calculate the total body load (TBL):
- TBL for digoxin = Dose (in mg) ingested x 0.8 (The value 0.8 reflects the bioavailability of digoxin)
- Step 2 – Number of vials = TBL/0.5
- (TBL/0.5 is identical to TBL x 2, which may be an easier calculation)

Steady state digoxin concentration is known — The number of Fab fragment vials needed for treatment when the concentration is known is calculated based upon the drug concentration and the patient's weight:

- Number of vials = [(serum digoxin concentration in ng/mL) (patient's weight in kg)]/ 100

Yeni

- Digoxin immune Fab for acute poisoning (except cardiac arrest):
- 2 vials IV initially and repeat 1 to 2 vials IV PRN guided by adequate perfusion and potassium <6 mmol/L
- 5 vials IV for cardiac arrest
- Life-threatening arrhythmia –calcium 30 mL IV
- Hyperkalaemia –insulin, glucose, bicarb, salbutamol

Therapeutic Guidelines

What's new in chronic digoxin accumulation?

- Correct precipitating factors

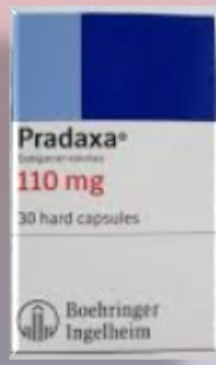
- Bradycardia alone –atropine, adrenaline, pacing
- **Bradycardia with hypotension** –digoxin immune Fab

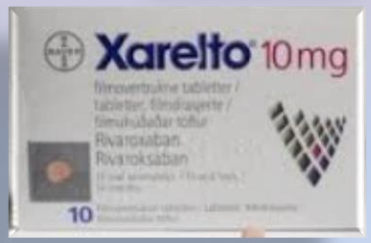
- Hyperkalaemia –as per acute digoxin poisoning

- Titrated digoxin immune Fab only in life-threatening arrhythmias or cardiac arrest
- 1 vial IV initially and repeat 1 vial IV PRN guided by adequate perfusion and potassium <6 mmol/L
- 2 vials IV for cardiac arrest

NOAC poisining and antidotes

- **Etki Mekanizması / Toksisite**
- Oral antikoagülanlar: direkt trombin inhibitörleri - dabigatran (Pradaxa)
  - Protrombinin fibrin matrisinin oluşumuna giden son yol olan trombine dönüşümünü önleyerek pıhtılaşmayı engeller.
- Oral antikoagülanlar: faktör Xa inhibitörleri - rivaroksaban (Xarelto), apixaban (Eliquis), edoksaban (Savaysa)
  - Trombin oluşumunu önlemek için faktör Xa'yı inhibe eder
- Ana toksisite nedenleri (kanamaya neden olur) kasıtlı aşırı doz ilaç alımı, azalmış ilaç klirensi veya travma
- Stabil bir pıhtı oluşturamama, küçük yaralanmalardan bile masif kanamaya neden olabilir





Farmakokinetik

Doğrudan trombin inhibitörleri (dabigatran)

Uygulamadan yaklaşık 2-3 saat sonra etki başlangıcı

24 saat antikoagülan etkisi ile 12 saatlik eliminasyon yarılanma ömrü

% 80 renal atılım

Faktör Xa inhibitörleri (rivaroksaban, apixaban, edoksaban)

Uygulamadan 2-4 saat sonra etki başlangıcı

Eliminasyon yarılanma ömrü 8-12 saattir, ancak Xa aktivitesi dozlamadan sonra 24 saate kadar taban çizgisine dönmez.

Hepatik ve renal atılım

Observational Study > Ann Emerg Med. 2016 Feb;67(2):189-95.
doi: 10.1016/j.annemergmed.2015.07.014. Epub 2015 Aug 19.

An Observational Study of the Factor Xa Inhibitors Rivaroxaban and Apixaban as Reported to Eight Poison Centers

Henry A Spiller [1], James B Mowry [2], Alfred Aleguas Jr [3], Jill R K Gr[iffith] [4], [5], Ryan [6], Stacey Bangh [7], Wendy Klein-Schwartz [8], Scott Schaeffer

- Tek ajan olarak Xa inhibitörü alımında kanama nadir
- İntihar girişiminde aşırı akut alımlar, önemli antikoagülasyona neden olabilir
- PT, PTT veya INR, vakaların küçük bir kısmında ↑, ancak kanama riskini ölçmek için güvenilmez
- Çocuklar tarafından tek doz yutulması toksisite ile ilişkilendirilmemiş

Study objective: Rivaroxaban and apixaban are part of a new group of oral anticoagulants targeting factor Xa and approved by the Food and Drug Administration in 2011 and 2012. These oral anticoagulants are administered at fixed daily doses, without the need for laboratory-guided adjustments. There are limited data available on supratherapeutic doses or overdose of the oral Xa inhibitors. This study characterizes the clinical effect in patients exposed to rivaroxaban and apixaban.

Methods: A retrospective study collected data from 8 regional poison centers covering 9 states. Cases were initially identified by a search of the poison centers' databases for case mentions involving a human exposure to Xarelto, rivaroxaban, Eliquis, or apixaban. Inclusion criteria included single-substance exposure. Exclusion criteria were animal exposure, polysubstance exposure, or information call. Data for the study were collected by individual chart review, including case narratives, and compiled into a single data set.

Results: There were 223 patients: 124 (56%) were female patients, mean age was 60 years, and 20 were children younger than 12 years (9%). One hundred ninety-eight patients ingested rivaroxaban (89%) and 25 ingested apixaban (11%). Dose was reported in 182 rivaroxaban patients, with a mean dose of 64.5 mg (range 15 to 1,200 mg), and in 21 apixaban patients, with a mean dose of 9.6 mg (range 2.5 to 20 mg). For rivaroxaban, prothrombin time was measured in 49 patients (25%) and elevated in 7; partial thromboplastin time, measured in 49 (25%) and elevated in 5; and international normalized ratio, measured in 61 (31%) and elevated in 13. For apixaban, prothrombin time was measured in 6 patients (24%) and elevated in none; partial thromboplastin time, measure in 6 (24%) and elevated in none; and international normalized ratio, measured in 5 patients (20%) and elevated in none. Bleeding was reported in 15 patients (7%): 11 rivaroxaban and 4 apixaban. The site of bleeding was gastrointestinal (8), oral (2), nose (1), bruising (1), urine (1), and subdural (1). The subdural bleeding occurred after fall and head injury. All cases with bleeding involved long-term ingestions. Coagulation test results were normal in most patients with bleeding: prothrombin time 5 of 6 (83%), partial thromboplastin time 5 of 6 (83%), and international normalized ratio 5 of 9 (55%). Blood products were used in 7 rivaroxaban patients (1 suicide) and 3 apixaban patients. No bleeding or altered coagulation test results occurred in children, which all involved a one-time ingestion. All 12 suicide attempts involved rivaroxaban: altered coagulation test results occurred for 5 patients (42%), no bleeding occurred in any suicide attempt patient, 1 patient was treated with fresh frozen plasma (international normalized ratio 12.47), and dose by patient history did not predict risk of altered coagulation or bleeding. Two rivaroxaban patients experienced elevation of hepatic transaminase levels greater than 1,000 U/L.

Conclusion: Bleeding after Xa inhibitor ingestion as a single agent is uncommon. Prothrombin time, partial thromboplastin time, or international normalized ratio may be elevated in a minority of cases but appears unreliable to measure risk of bleeding. Massive acute ingestion in suicide attempt may result in significant anticoagulation. Single exploratory ingestion by children was not associated with toxicity. [Ann Emerg Med. 2015;■:1-7.]

NOAC KULLANAN HASTA

Kanama **VAR**

Hayati tehdit eden kritik organ kanaması, veya maksimum destek tedaviye yanıt vermeyen majör kanama

Geri döndürücü ajan önerilir

Dabigatran

1. tercih idarucizumap 5 g IV

yoksa

2. terciz APCC 50 U/kg IV

Xa inhibitörü

1 tercih andexanet alfa (doz için bknz KÖ3)

yoksa

2.tercih 4FPCC 2000 U.

Diğer kanamalar

Geri döndürücü ajan önerilmez

NOAC KULLANAN HASTA

COVID-19: Therapeutics and Their Toxicities

- Viral Entry Inhibitors
- Chloroquine and Hydroxychloroquine
- APN01
- Leronlimab (PRO 140)

- Viral Replication Inhibitors
- Remdesivir and Favipiravir
- Lopinavir-Ritonavir

- Diğerleri
- Azithromycin
- Convalescent Plasma

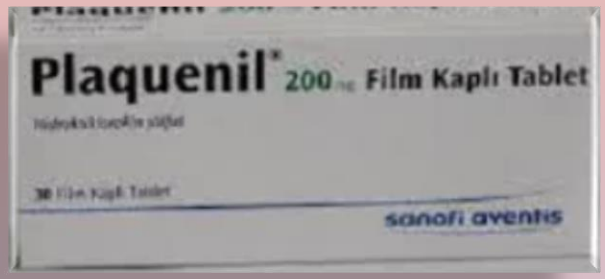
J Med Toxicol. 2020 Jul; 16(3): 284–294. PMCID: PMC7192319
Published online 2020 Apr 30. doi: 10.1007/s13181-020-00777-5 PMID: 32356252

COVID-19: Therapeutics and Their Toxicities

Michael A. Chary,[1,2,3] Alexander F. Barbuto,[1,2,3] Sudeh Izadmehr,[4] Bryan D. Hayes,[5] and Michele M. Burns[1,2]

Author information · Article notes · Copyright and License information Disclaimer

Chloroquine
Hydroxychloroquine



- Klorokin, başlıca birkaç *Plasmodia* türünün neden olduğu bulaşıcı bir hastalık olan sıtmayı tedavi etmek için kullanılan bir 4-aminokinolin

- Klorokin, SARS-CoV-1 enfeksiyonunu inhibe ettiği bulunmuştur ve SARS-CoV-1 ve SARS-CoV-2 arasındaki sekans ve yapı homolojileri, klorokin'in SARS-CoV-2 enfeksiyonunu azaltabileceğini düşündürmektedir

Chloroquine and Hydroxychloroquine toxicity

- Klinik
- Asgari ölümcül hidroksiklorokin dozu iyi tanımlanmamış
- Şiddetli semptomları (hipotansiyon, hipokalemi ve ventriküler disritmiler) ortaya çıkardığı bildirilen minimum doz 4 gr
- 5 gr↑, ventriküler disritmiler ve hipokalemiye bağlı mortalite ile ilişkili
- Aşırı dozdan 1-3 saat sonra derin hipotansiyon ; sodyum kanal blokajı EKG'de QRS genişlemesi
- Nörolojik etkiler arasında nöbetler ve CNS depresyonu
- Potasyum kanal blokajı, uzamış QTc aralığı ve TdP ile sonuçlanabilir ve klorokin toksisitesi mevcutsa QT uzatan ajanları kullanmaktan kaçınmalı

- Tedavi
- Semptomatik
- Spesifik antidot yok
- Hipokalemi tedavisi
- Hipotansiyon için vazopresörler
- Nöbet varsa benzodiazepin
- Geniş QRS varsa NaHCO3
- İntravenöz lipit

Riou B. Treatment of severe chloroquine poisoning. N Engl J Med. 1988 Jan 7;318(1):1–6.
Crouzette J,. Experimental assessment of the protective activity of diazepam on the acute toxicity of chloroquine. J Toxicol Clin Toxicol. 1983 May;20(3):271–9.
Ten Broeke R, Early treatment with intravenous lipid emulsion in a potentially lethal hydroxychloroquine intoxication. Neth J Med. 2016 Jun;74(5):210–4

Remdesivir ve Favipiravir

- Nükleotid Analogları; yeni viral RNA üretimini durdurmak ve enfekte konakçı hücrelerin yeni viryonlar için üretim yerleri haline gelmesini engellerler
- Remdesivir veya favipiravir toksisitesi ile ilgili veri yok, diğer nükleozid analogları için bildirilen toksisiteden çıkarım yapılmakta

- Toksisistesi
- Uzun süre terapatik kullanımlarda Metabolik asidoz gözlenmiş
- Akut çok miktarda alımlarda artmış laktatlı şiddetli metabolik asidoz
- Periferik nöropati
- Kemik iliği baskılanması
- Pankreatit ve miyopati

- Tedavi
- Destek ve semptomatik tedavi
- Spesifik bir antidot yoktur, ancak bazıları tiamin, riboflavin, 1 -karnitin ve C vitamini gibi mitokondriyal kofaktörlerle tedavinin hastaların iyileşmesine yardımcı olabileceğini öne sürmektedir

Falco V,, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. Clin Infect Dis. 2002 Mar 15;34(6):838–46.
ohnson AA, et al. Toxicity of antiviral nucleoside analogs and the human mitochondrial DNA polymerase. J Biol Chem. 2001 Nov 2;276(44):40847–57

Lopinavir-Ritonavir

- Ritonavir, lopinavire bir farmakokinetik güçlendirici olarak eklenir; ritonavir, lopinaviri inaktive eden enzim olan sitokrom CYP 3A4'ün güçlü bir inhibitörü

- Toksisitesi
- Tedavi dozunda mide bulantısı ve kusmanın yanı sıra hafif transaminaz yükselmeleri
- Rutin kullanımda ilimli transaminaz artışı
- Bir çalışmada da bu kombinasyonu alan birçok hasta bulantı, kusma ve ishal nedeniyle çalışmadan ayrıldı.

- Aşil tendinopati, lopinavir-ritonavir alan bireylerde, maruziyet sonrası profilaksi için kısa süreli kullanımda bile bildirilmiş

Cao B,et al. A trial of Lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020 Mar 18.
Cresswell F V, Achilles tendinopathy following Kaletra (lopinavir/ritonavir) use. Int J STD AIDS. 2014 Oct;25(11):833–5

Azitromisin

- Ana toksisitesi, potasyum kanalı blokajı nedeniyle kardiyak disritmilere yol açan QTc uzaması

- Bir çalışmada, 5 günlük bir azitromisin, diğer antibiyotiklere kıyasla kardiyovasküler ölümde yaklaşık üç kat ↑ancak benzer büyüklükte bir takip kohort çalışması ve prospektif randomize kontrollü çalışmaların meta-analizi mortalitede artmış risk yok

- Azitromisin ve klorokin veya hidroksiklorokin kombinasyonunun, tek başına kardiyak disritmileri tetikleme olasılığının daha yüksek olabilir

Goldstein EJC, Antimicrobial-associated QT interval prolongation: pointes of interest. Clin Infect Dis. 2006 Dec 15;43(12):1603–11. Ray WA,. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012 May 17;366(20):1881–90.

Teşekkürler