akdeniz acil tıp

# KARDİYOTOKSİK AJANLARLA ZEHİRLENME, EKG ve LİPİD TEDAVİLERİ

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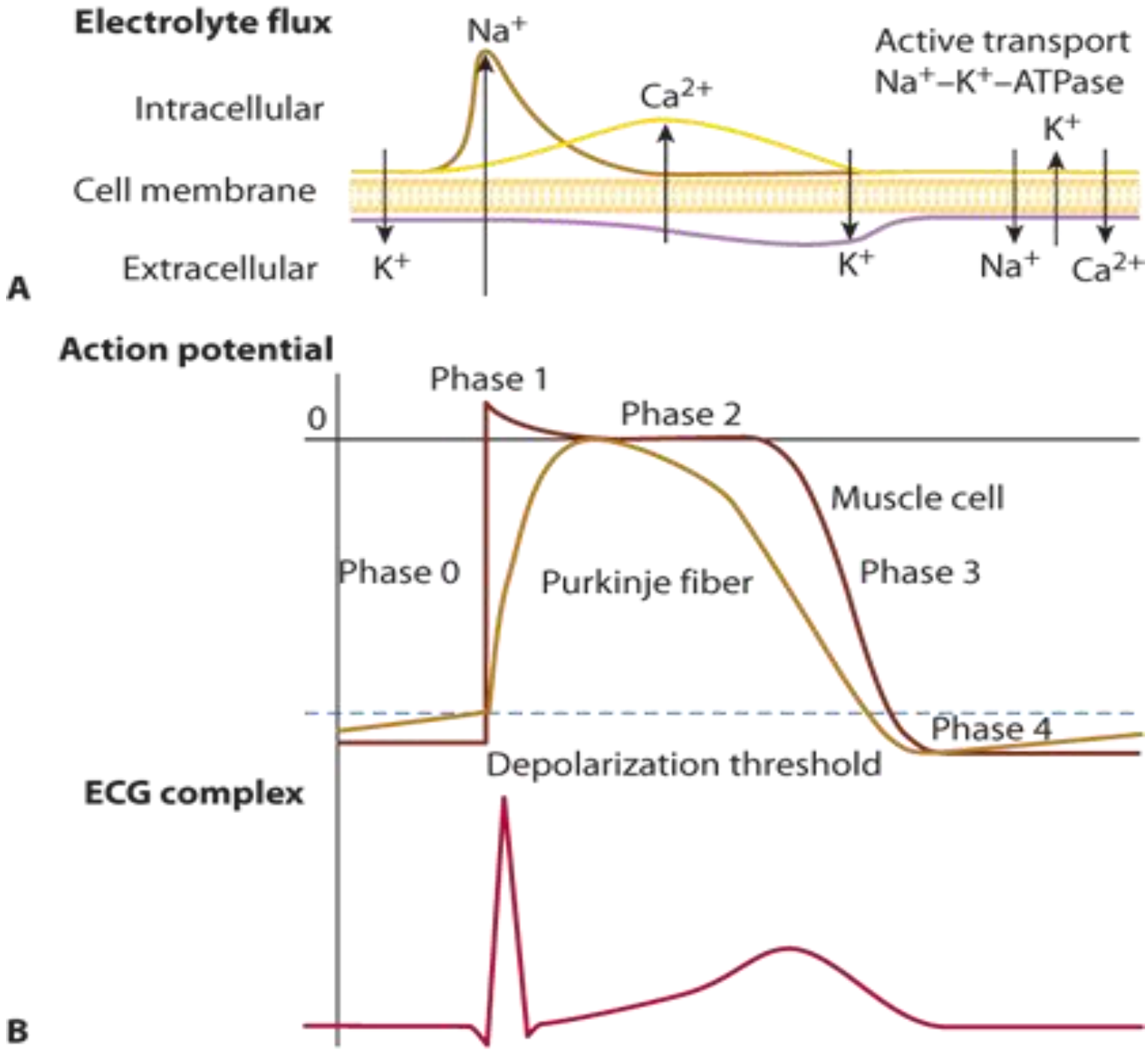
ANTALYA

# Plan

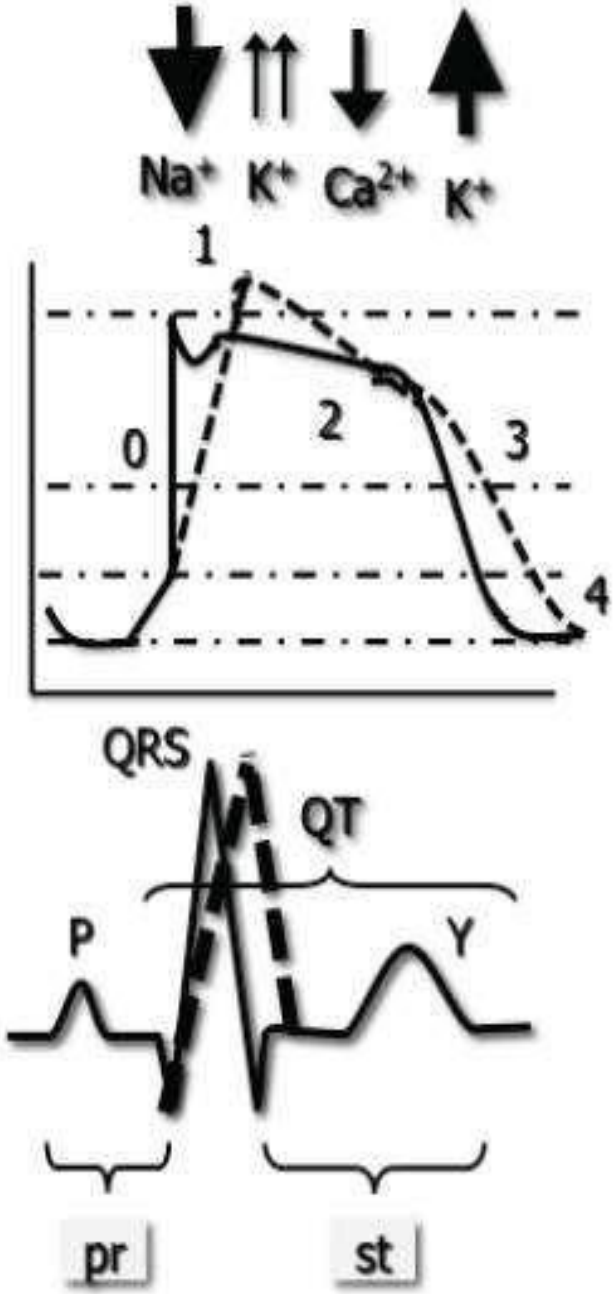
- Kardiyotoksik Ajanlar nelerdir
- Kardiyotoksik Ajanların elektrofizyolojik etkilerinin ortaya çıkışı
- Sık karşılan ajanlar ve tedavi seçenekleri

# Toksinlerin Kardiyotoksik Etki Mekanizmaları

- **Membran Depressan Etki**
  - Na Kanal Blokajı
  - K Kanal Blokajı
  - Ca Kanal Blokajı
  - Na-K ATPase Blokajı
- **Otonomik Sinir Sistemine Etkisi**
  - Beta Adrenerjik Blokörler
  - Sempatik inhibitörler, antikolinerjikler ve kolinerjikler
- **Diğer**


Electrolyte flux
Intracellular
Cell membrane
Extracellular
Na+
Ca2+
Active transport
Na+–K+–ATPase
K+
K+
K+
Na+
Ca2+
A
Action potential
Phase 1
0
Phase 2
Muscle cell
Phase 0
Purkinje fiber
Phase 3
Phase 4
Depolarization threshold
ECG complex
B

# Sodium channel blockade

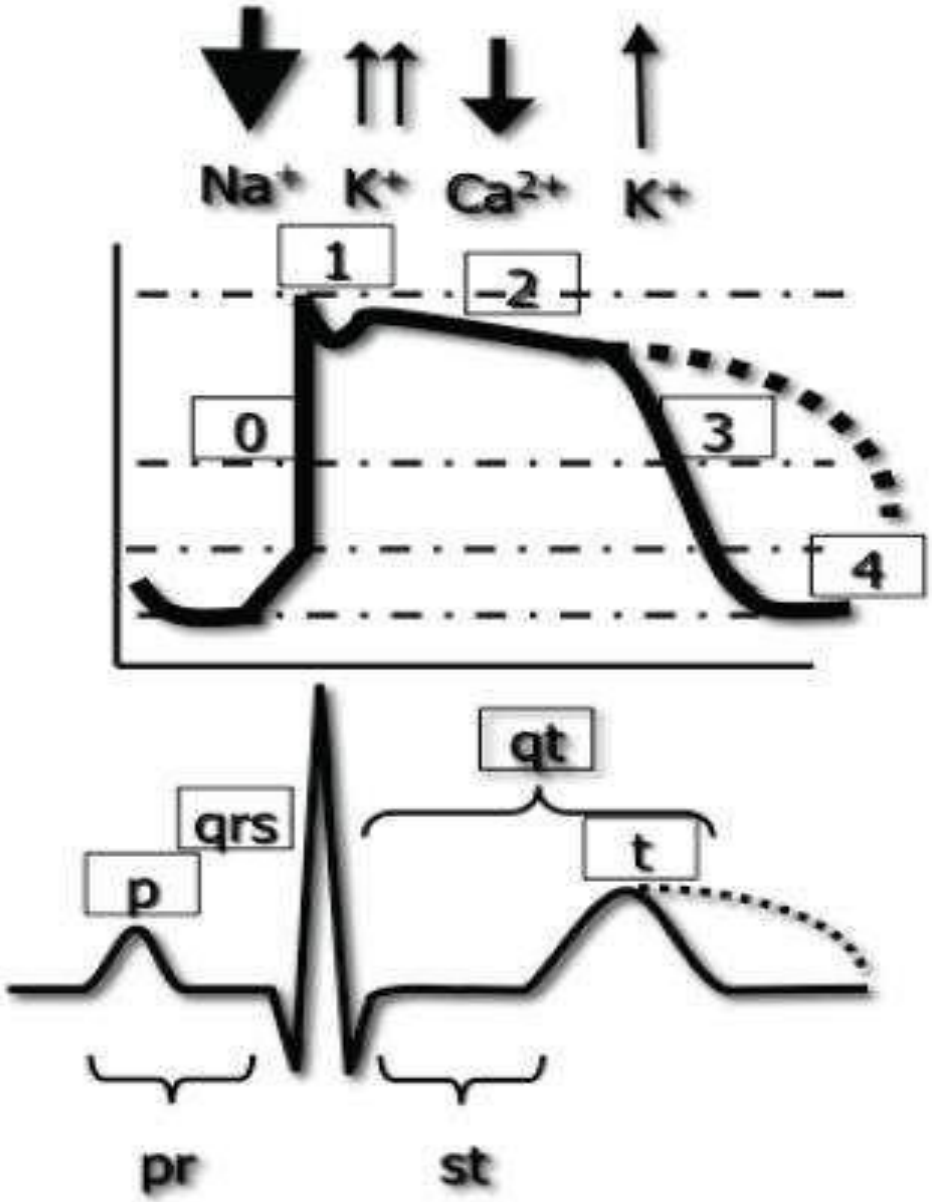



- Na kanal blokajı ile Faz 0 eğimi azalır
- QRS Genişlemesi
- Ventriküler taşikardi
- Asistoli

# Na Kanal Blokajı Yapan Ajanlar

| | |
|---|---|
| Inhibitors of fast $Na^+$ channels | 1. Cardiovascular drugs:<br>- Type Ia antiarrhythmics (Quinidine, Disopyramide, Procainamide)<br>- Type Ic antiarrhythmics (Flecainide, Encainide, Propafenone, Moricizine)<br>- Propranolol and other membrane depressant beta-blockers*<br>- Verapamil, Diltiazem<br>2. Psychiatric drugs:<br>- Carbamazepine<br>- Cyclic antidepressants (Amitriptyline, Amoxapine, Desipramine, Doxepin, Imipramine, Nortriptyline, Maprotiline)<br>- Neuroleptics (Thioridazine, Mesoridazine)<br>- Other antidepressants (Citalopram)<br>- Antipsychotics (Loxapine)<br>3. Other drugs:<br>- Amantadine<br>- Antihistamines (Diphenhydramine)<br>- Chloroquine, Hydroxychloroquine<br>- Orphenadrine<br>- Narcotic pain relievers (Propoxyphene)<br>4. Illicit drugs: Cocaine<br>5. Toxins: Quinine, Saxitoxin, Tetrodotoxin |

# $K^+$ Channel Blockade



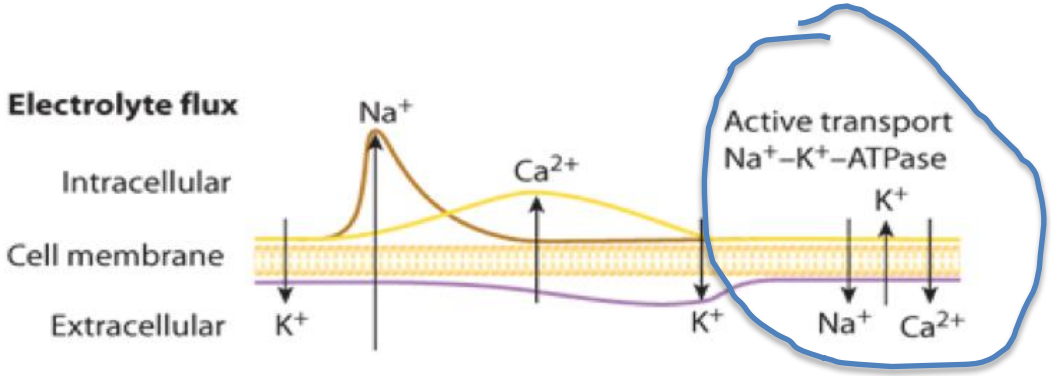

- Faz II ve Faz III uzar
- Uzun QT sendromu ve Torsades de Pointes

# K Kanal Blokajı Yapan Ajanlar

| | |
|---|---|
| Inhibitors of outward $K^+$ channel | 1. Cardiovascular drugs:<br>- Class IA antidysrhythmics**(Disopyramide, Quinidine, Procainamide)<br>- Class IC antidysrhythmics (Encainide, Flecainide, Moricizine, Propafenone)<br>- Class III antidysrhythmics** (e.g. Amiodarone, Dronedarone, Dofetilide, Ibutilide, Sotalol, Vernakalant)<br>- Anti-anginal/vasodilators*,** (Bepridil, Prenylamine, Terodiline)<br>- Antihypertensives (Ketanserin*)<br>2. Psychiatric drugs:<br>- Antipsychotics (Chlorpromazine, Droperidol, Haloperidol, Mesoridazine, Pimozide, Quetiapine, Risperidone, Thioridazine, Ziprasidone)<br>- Cyclic antidepressants (Amitriptyline, Amoxapine, Desipramine, Doxepin, Imipramine, Nortriptyline, Maprotiline)<br>- Other antidepressants (Citalopram, Venlafaxine)<br>- Phenothiazines<br>3. Other drugs:<br>- Antihistamines (Astemizole, Diphenhydramine, Loratidine, Terfenadine*, Hydroxyzine)<br>- Serotonin 5-$HT_4$ receptor agonist (Cisaprid*,**)<br>- Antimicrobials and antimalarics (Ciprofloxacin, Gatifloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin, Clarithromycin**, Erythromycin**, Pentamidine**, Chloroquine**, Halofantrine, Hydroxychloroquine, etc.)<br>- Arsenic trioxide<br>- Probucol*<br>4. Synthetic opioids: Levomethadyl<br>5. Opium alkaloids: Papaverine**<br>6. Toxins: Quinine, Organophosphates (fig.10) |

# Na–K ATPase blokörleri

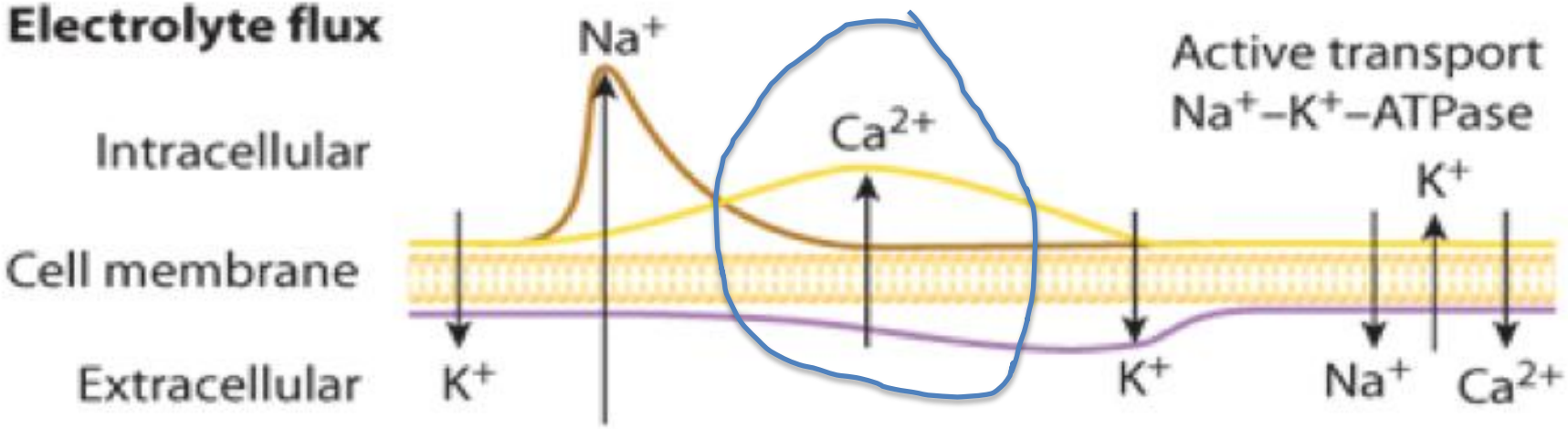
- Kardiyak Glikozidler (Na+/K+ATPase) pompasını inhibe eder
- Sonuçta; Na+ ve  K+'ın hücre membranından geçişi inhibe olur→hücre içi Na+ artar ve Na+/Ca2+ pompası sekonder olarak aktive olur→Hücre içi Ca2+ düzeyi artar→pozitif inotropik etki oluşur
- Kardiyak glikozidler vagal tonusu arttırarak AV nodal depresyona da neden olabilir



# Na–K ATPase blokörleri

| | |
|---|---|
| $Na^+/K^+$ ATPase blockers | 1. Drugs:<br>- Digoxin (Lanoxin)<br>- Digitoxin<br>2. Plants producing cardiac glycosides:<br>- Cardenolide type: *Strophanthus* – ouabain g/k/e-strophanthin, *Digitalis lanata* and *Digitalis purpurea* (foxglove) – digoxin, digitoxin, *Nerium oleander* (oleander) – oleandrin, *Convallaria majalis* (Lily of the valley), *Apocynum cannabinum* (Dogbane), *Asclepias species*.<br>- Bufadienolide type: *Urginea maritima* (Red squill)<br>3. Animals producing cardiac glycosides:<br>- Bufadienolide type: *Bufo marinus* toads |

# Kalsiyum Kanal Blokajı




- KKB hücre içine kalsiyum girişini azaltır
  - Kardiyak;
    - Bradikardi, (-) İE ve kardiyak output azalır
  - Vasküler;
    - Vasodilatasyon

# Ca Kanal Blokajı Yapan Ajanlar

| | |
|---|---|
| Inhibitors of slow $Ca^{2+}$ channels | 1. Dihydropyridines:<br>- 1st generation: Nicardipine, Nifedipine<br>- 2nd generation: Felodipine, Isradipine, Nimodipine<br>- 3rd generation: Amlodipine, Nitrendipine<br>- 4th generation: Lercanidipine, Lacidipine<br>2. Phenylalkylamine:<br>- Verapamil<br>- Gallopamil<br>3. Benzothiazepine:<br>- Diltiazem<br>4. Non-selective:<br>- Bepridil<br>- Mibefradil<br>- Fluspirilene |

# Beta-adrenerjik blokör toksisitesi

- β1 → (-) İE ve KE, AV blok
- β2 → Glikokojenoliz/glikoneogenez de azalma, kan damarları/bronş/gis düz kaslarında gevşeme
- β3 → Lipid metabolizmasından sorumlu
- **Klinik, tanı ve tedavi yönünden KKB ne benzerdir.**
  - **Diyaliz etkisiz:** Propanolol, metoprolol, timolol
  - **Diyaliz etkili:** Atenolol, nadolol, sotalol, acebutolol

# KARDİYOTOKSİK AJANLARLA ZEHİRLENMELER İLE HANGİ SIKLIKTA KARŞILAŞIYORUZ?

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## 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report

David D. Gummin, James B. Mowry, Daniel A. Spyker, Daniel E. Brooks, Michael O. Fraser & William Banner

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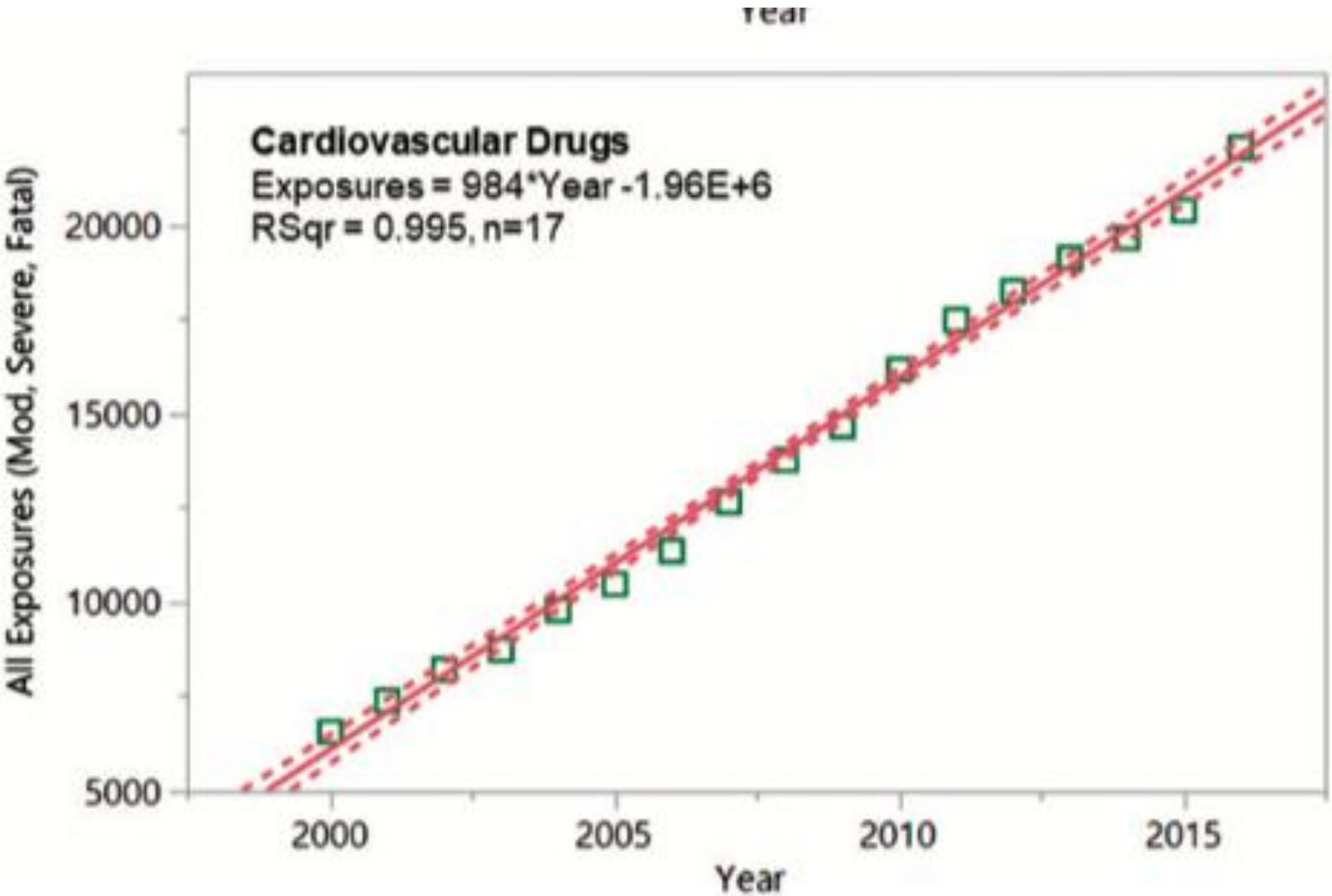
# Görülme Sıklığı



# Erişkinlerde

Table 17(F). Substance categories most frequently identified in drug identification calls (top 25).

| Substance (major generic category) | All substances | %[a] |
|---|---|---|
| Analgesics | 57,281 | 35.00 |
| Sedative/hypnotics/antipsychotics | 29,468 | 18.01 |
| Unknown drug | 9808 | 5.99 |
| Cardiovascular drugs | 9681 | 5.92 |
| Antidepressants | 8329 | 5.09 |
| Muscle relaxants | 7520 | 4.59 |
| Anticonvulsants | 6301 | 3.85 |
| Antihistamines | 6274 | 3.83 |
| Stimulants and street drugs | 5634 | 3.44 |
| Antimicrobials | 5362 | 3.28 |
| Information calls | 4652 | 2.84 |
| Hormones and hormone antagonists | 3390 | 2.07 |
| Gastrointestinal preparations | 3335 | 2.04 |
| Diuretics | 1984 | 1.21 |
| Miscellaneous drugs | 1329 | 0.81 |
| Cold and cough preparations | 787 | 0.48 |
| Anticholinergic drugs | 396 | 0.24 |
| Asthma therapies | 395 | 0.24 |
| Anticoagulants | 383 | 0.23 |
| Electrolytes and minerals | 350 | 0.21 |
| Vitamins | 314 | 0.19 |
| Dietary supplements/herbals/homeopathic | 108 | 0.07 |
| Other/unknown nondrug substances | 103 | 0.06 |
| Narcotic antagonists | 82 | 0.05 |
| Antineoplastics | 66 | 0.04 |

[a]Percentages are based on the total number of substances reported in all drug identification calls ($N = 163{,}663$).

# Çocuklarda

Table 17(E). Substance categories most frequently involved in pediatric (≤ 5 years) deaths[a]

| Substance (major generic category) | All substances | %[b] | Single substance exposures | %[c] |
|---|---|---|---|---|
| Fumes/gases/vapors | 12 | 18.18 | 8 | 21.62 |
| Analgesics | 11 | 16.67 | 9 | 24.32 |
| Cardiovascular drugs | 7 | 10.61 | 1 | 2.70 |
| Antidepressants | 6 | 9.09 | 1 | 2.70 |
| Antihistamines | 5 | 7.58 | 3 | 8.11 |
| Batteries | 4 | 6.06 | 4 | 10.81 |
| Unknown drug | 4 | 6.06 | 4 | 10.81 |
| Stimulants and street drugs | 3 | 4.55 | 1 | 2.70 |
| Chemicals | 2 | 3.03 | 0 | 0.00 |
| Pesticides | 2 | 3.03 | 1 | 2.70 |
| Plants | 2 | 3.03 | 2 | 5.41 |
| Sedative/hypnotics/antipsychotics | 2 | 3.03 | 0 | 0.00 |
| Alcohols | 1 | 1.52 | 1 | 2.70 |
| Antimicrobials | 1 | 1.52 | 0 | 0.00 |
| Cosmetics/personal care products | 1 | 1.52 | 1 | 2.70 |
| Dietary supplements/herbals/homeopathic | 1 | 1.52 | 1 | 2.70 |
| Diuretics | 1 | 1.52 | 0 | 0.00 |
| Hormones and hormone antagonists | 1 | 1.52 | 0 | 0.00 |
| Total | 66 | 100.00 | 37 | 100.00 |

[a]Includes all children with actual or estimated ages ≤5 years old. Results do not include "unknown child" or "unknown age". Includes death and death, indirect regardless of RCF.
[b]Percentages are based on the total number of substances reported in pediatric fatalities ($N = 66$).
[c]Percentages are based on the total number of single substance pediatric fatalities ($N = 37$).

# Mortalite

Table 18. Categories associated with largest number of fatalities (top 25)[a].

| Substance (minor generic category) | All substances | %[b] | Single substance exposures | %[c] |
|---|---|---|---|---|
| Miscellaneous sedative/hypnotics/antipsychotics | 416 | 12.20 | 15 | 2.53 |
| Opioids | 283 | 8.30 | 38 | 6.41 |
| Miscellaneous stimulants and street drugs | 260 | 7.62 | 68 | 11.47 |
| Miscellaneous alcohols | 237 | 6.95 | 17 | 2.87 |
| Acetaminophen alone | 184 | 5.39 | 73 | 12.31 |
| Calcium antagonists | 142 | 4.16 | 19 | 3.20 |
| Acetaminophen combinations | 129 | 3.78 | 36 | 6.07 |
| Beta blockers | 115 | 3.37 | 11 | 1.85 |
| Selective serotonin reuptake inhibitors (SSRI) | 102 | 2.99 | 1 | 0.17 |
| Miscellaneous antihistamines | 95 | 2.79 | 11 | 1.85 |
| Miscellaneous antidepressants | 92 | 2.70 | 9 | 1.52 |
| Miscellaneous unknown drug | 89 | 2.61 | 23 | 3.88 |
| Miscellaneous fumes/gases/vapors | 80 | 2.35 | 47 | 7.93 |
| Hypoglycemic, single agent | 72 | 2.11 | 10 | 1.69 |
| Tricyclic antidepressants (TCA) | 66 | 1.93 | 20 | 3.37 |
| Acetylsalicylic acid alone | 65 | 1.91 | 18 | 3.04 |
| Miscellaneous anticonvulsants | 64 | 1.88 | 2 | 0.34 |
| Nonsteroidal antiinflammatory drugs | 64 | 1.88 | 9 | 1.52 |
| Miscellaneous cardiovascular drugs | 62 | 1.82 | 21 | 3.54 |
| Miscellaneous muscle relaxants | 61 | 1.79 | 6 | 1.01 |
| Anticonvulsants: gamma aminobutyric acid and analogs | 60 | 1.76 | 3 | 0.51 |
| Serotonin norepinephrine reuptake inhibitors (SNRI) | 51 | 1.50 | 3 | 0.51 |
| Miscellaneous chemicals | 47 | 1.38 | 17 | 2.87 |
| Angiotensin converting enzyme inhibitor | 39 | 1.14 | 0 | 0.00 |
| Cannabinoids and analogs | 32 | 0.94 | 0 | 0.00 |

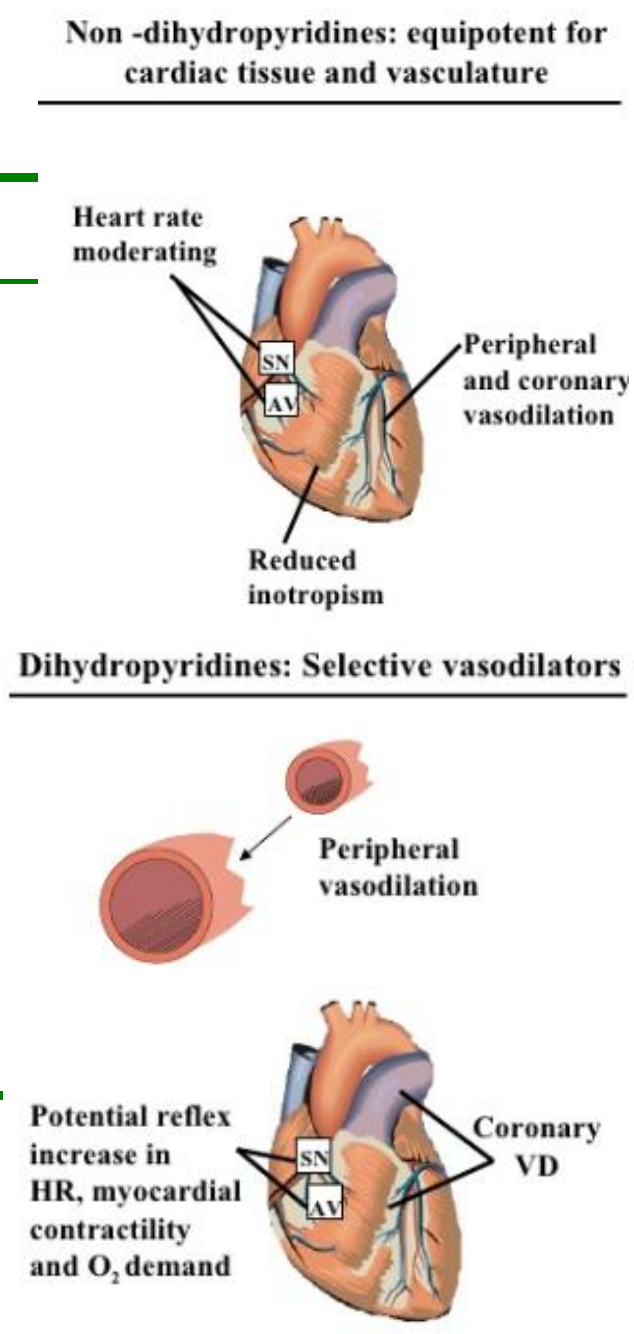
[a]Numbers represent total exposures associated with 1415 fatalities (with RCF of 1 – undoubtedly responsible, 2 – probably responsible, or 3 – contributory); each fatality may have had exposure to more than one substance.
[b]Percentages are based on the total number of substances reported in fatal exposures ($N = 3411$).
[c]Percentages are based on the total number of single substance fatal exposures ($N = 593$).

# Kalsiyum Kanal Blokeri İntoksikasyonları

# Giriş

- Kullanıldığı yerler; (1964 tanımlanmış, **1970** klinik kullanım-Verapamil)
  - KVS;
    - Hipertansiyon,
    - Anjina pektoris,
    - Disritmiler,
  - Diğer;
    - Migren profilaksisi,
    - Raynoud fenomeni ve
    - Subaraknoid kanama
- Son 5 yılda; >50.000 vaka, >100 ex

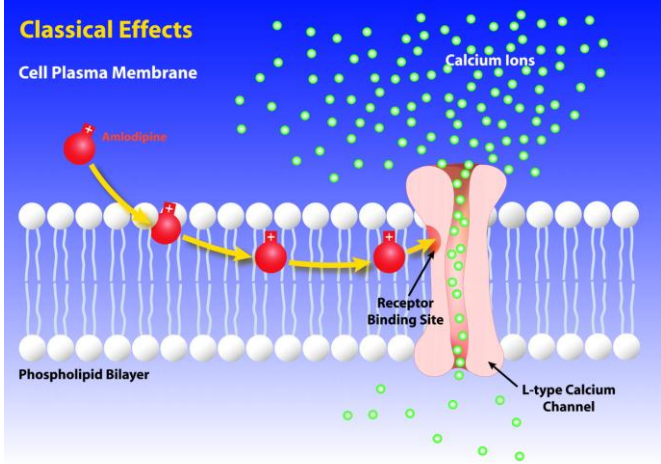
| Sınıf | Spesifik Madde |
|---|---|
| Fenilalkilamin | Verapamil |
| Benzothiazepin | Diltiazem |
| Dihidropiridinler | Nifedipin<br>Isradipin<br>Amlodipin<br>Felodipin<br>Nimodipin<br>Nisoldipin<br>Nicardipin |
| Diarilaminopropilamin ether | Bepridil |



# Farmakokinetik

- Tüm KKB'ler oral yoldan iyi emilirler
  - sitokrom P450 mikroenzim ile hepatik yoldan metabolize edilir
- Yüksek oranda proteine bağlanır
- Geniş volüm distribüsyonu vardır
  - **hemodiyaliz ve hemoperfüzyonla kandan temizlenemez**

# Patofizyoloji




- Kalsiyum, hücre içine "**Ca-spesifik voltaj duyarlı kanallar**" ile girer
  - P, N, R, T, Q ve L-tipi kanallar
  - **L tipi Ca kanalları**: tüm kas hücre membranlarında vardır
- $L_{1c}$ alt ünitesi; KKB' lerin hepsi buraya bağlanır ve kalsiyum transportunu engeller

# Klinik

- Kardiyodepresif bir toxidrom
  - Azalmış kalp hızı (**Bradikardi**)
  - Düşük kan basıncı (**Hipotansiyon**)
- Çocuklarda tek doz semptomatik olabilir
  - Ölüme dahi neden olabilir
  - Hiperglisemi ve akut pulmoner hasar bildirilmiş

# Klinik – Fizik muayene

- Bilinç ve kardiyovasküler duruma odaklanın:
  - Hipotansiyon
  - Bradikardi, değişken derecede kalp blokları
  - Bilinç değişikliği veya nöbet
    - Hipotansiyona sekonder
  - Bağırsak infarktı – nadir olgularda
    - Mezenterik perfüzyon azalmasına bağlı

# Tanısal Tetkikler

- 12 derivasyon EKG
- Hipoperfüzyon nedeni ile:
  - Akciğer grafisi
  - Puls-oksimetre
- Metabolik asidoz için
  - Serum biyokimya tetkikleri
- Elektrolitler
- Serum glukoz

# Tedavi

## Hastane öncesi

- ABC
- Damar yolu, oksijen, monitör
- SF infüzyonu → KKY yoksa
- Atropin denenebilir → hemodinamik olarak ciddi bradikardi varsa

# Tedavi

- <u>Gastrointestinal dekontaminasyon</u>
  - **Gastrik lavaj**
    - İlk 1-2 saatte
    - Yavaş salınımlı tabletlerde
  - **Aktif kömür**
    - 1 gr/kg dozunda
    - Yavaş salınımlı tabletlerde 0.5 mg/kg' dan tekrarlayan doz
  - **Tüm barsak irrigasyonu**
    - Polietilen glikol ile yapılır
    - Özellikler yavaş salınımlı tabletlerde etkilidir
    - 1-2lt/st' den olacak şekilde, çocuklarda üst doz 500 ml/st

# Tedavi

- <u>Başlangıç tedavisi:</u>
  - Sıvı
  - Atropin
  - Hasta stabil değilse, birden fazla farmakolojik ajan aynı anda başlanabilir

- <u>Farmakolojik ajanlar</u>
  - Atropin
  - Kalsiyum
  - İnsülin
  - Glukagon
  - Adrenerjik ajanlar
    - İzoproterenol
    - Dopamin
    - Epinefrin
    - Norepinefrin
  - Lipid emülsiyon
  - Diğer
    - Fosfodiesteraz inhibitörleri
    - Metilen mavisi
    - Levosimendan
    - L-Carnitin

# Atropin

- Semptomatik bradikardilerde endikedir
- Ciddi zehirlenmelerde yetersiz kalır
- **Dozu:**
  - 0.5 mg her 3-5 dakikada bir
  - Üst doz 3 mg
  - Çocuklarda 0.02 mg/kg
- Tüm barsak irrigasyonu yapılan hastalarda antikolinerjik etkilerine dikkat edilmelidir

# Kalsiyum

- KKB aşırı alımlarında önemli basamaklardan birisidir
- Kalp hızından çok, kontraksiyonu artırır
  - Negatif inotropiyi
  - Bozulmuş iletiyi
  - Hipotansiyonu düzeltir
- Etki kısa sürelidir ve ciddi zehirlenmelerde yetersiz kalır

# Kalsiyum

- **<u>Doz</u>**
  - 13-25 mEq IV bolus
    - 10-20 mL %10 kalsiyum klorid ($CaCl_2$) veya 30-60 mL %10 kalsiyum glukonat
  - 0.2-0.4 ml/kg/st $CaCl_2$ veya 0.6-1.2 ml/kg/st Ca glukonat infüzyon
- Tekrarlayan dozlarda hiperkalsemi veya hiperfosfatemi riski vardır
- **<u>Yan etkileri:</u>**
  - Kalsiyum klorid: geniş damar yolundan verilmeli-nekroz
  - Bulantı, kusma, sıcak basması (flashing), konstipasyon, konfüzyon, anjina.

# İnotrop ve vazopressörler

- Kalsiyum uygulamasına cevap vermeyen veya tekrarlayan dozlara ihtiyac duyan hastalara genellikle adrenerjik agonistler verilir.
- Dopamin, epinefrin, norepinefrin, vazopressin, dobutamin ve isoprotrenole cevap veren kalsiyum kanal blokeri zehirlenmeleri rapor edilmiştir.

# İnsülin - Glikoz

- Ciddi zehirlenmesi olan hastalarda hiperinsülinemi / öglisemi en ümit verici tedavidir
- Yüksek doz insülinin pozitif inotrop etkisi vardır
  - Hücre içine kalsiyum girişinde artış
  - Miyokardın karbonhidrat kullanımında artış

# Yüksek doz insülin - Glikoz

- **<u>Tedavi:</u>**
  - 1 U/kg/st bolus insülin ve 0.5-1 U/kg/st infüzyon
  - 200ml/saat (erişkin) veya 5ml/kg/saat (çocuk) hızında %10 glikozun sudaki solüsyonunu (0.1 gr/ml)
  - Hasta öglisemik olacak şekilde tedavi idame ettirilir
  - Etkisinin ortaya çıkması 30-60 dakika alacağı için başlangıçta hipotansiyonu engellemek için pozitif inotrop ve vazopressör başlanabilir

# Glukagon

- Pankreastan, hipoglisemi ve katekolaminlere cevap olarak salınır
- İnotropik ve kronotropik etkileri vardır
- Beta reseptörleri by-pass ederek, $G_s$ proteini aracılığı ile adenilat siklazı aktive eder ve hücre içi kalsiyum girişini artırır
- 3-5 mg glukagon 1-2 dakikada IV infüzyon, 5 dakika içinde yanıt alınamaz ise 4-10 mg ek doz
- Etkinin görüldüğü dozdan saatlik infüzyona devam edilir

# Lipid Emülsiyon Tedavisi

- Standart tedaviye yanıt vermeyen uzamış salınımlı verapamil alımı olgularında faydalı olduğunu bildirilmiş
- Etki mekanizması:
  - Yağda çözünen ilaçlar için farmakolojik bir sünger oluşturur
  - Kardiyak enerji ihtiyacını karşılar
  - Hücre içi kalsiyum seviyesini arttırarak miyosit fonksiyonunu iyileştirir

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REVIEW

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

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**Table 2.** Strength of recommendation and level of evidence.

**Strength of recommendation (consensus-based)**

Level 1: Strong recommendation (The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.)

Level 2: Weak/conditional recommendation (The course of action is considered appropriate by the majority of experts but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.)

*Neutral position*: The course of action is neither preferred nor rejected by the majority of experts; either due to a balance in the desirable and undesirable effects of adherence to the recommendation or due to major uncertainties to its evaluation.

*No recommendation*: The group of experts reached no agreement

**Level of evidence (GRADE system)**

Grade A: High level of evidence (The true effect lies close to our estimate of the effect.)

Grade B: Moderate level of evidence (The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.)

Grade C: Low level of evidence (The true effect may be substantially different from our estimate of the effect.)

Grade D: Very low level of evidence (Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect.)

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

| Toxins | Clinical situations (strength of recommendation & level of evidence)[a] |
|---|---|
| *Local anesthetics* | |
| Bupivacaine | In cardiac arrest: we recommend using ILE (1D)<br>In life-threatening toxicity: we suggest using ILE as part of treatment modalities (2D) and we recommend using ILE if other therapies fail/in last resort (1D)<br>In non-life-threatening toxicity: neutral recommendation |
| All other local anesthetics | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D)<br>In non-life-threatening: neutral recommendation |
| *Non-local anesthetics* | |
| Antidysrhythmics Class 1 | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: neutral recommendation<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Amitriptyline | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE as part of treatment modalities (2D) |
| Other tricyclic antidepressants | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE in any circumstances (2D) |
| Baclofen | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: neutral recommendation<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Beta receptor antagonists (Lipid-soluble) | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: neutral recommendation<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Beta receptor antagonists (Non lipid-soluble) | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D) |
| Bupropion | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest using ILE if other therapies fail/in last resort (2D), but we suggest not using ILE as first-line therapy (2D) |

| | |
|---|---|
| Calcium channel blockers: Diltiazem and verapamil | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Calcium channel blockers: Dihydropyridines | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE in any circumstances (2D) |
| Cocaine | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D) |
| Diphenhydramine | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we recommend not using ILE as first-line therapy (1D) and we suggest not using ILE otherwise (2D) |
| Other antihistamines | Insufficient data |
| Ivermectin | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: neutral recommendation<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Other insecticides | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Lamotrigine | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) nor as part of treatment modalities (2D) |
| Malathion | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Other pesticides | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Olanzapine | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: neutral recommendation<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Other antipsychotics | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: we suggest not using ILE as first-line therapy (2D)<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |
| Selective serotonin reuptake inhibitors | In cardiac arrest: neutral recommendation<br>In life-threatening toxicity: neutral recommendation<br>In non-life-threatening toxicity: we suggest not using ILE as first-line therapy (2D) |

[a]Neutral position if not otherwise specified.

# ILE Tedavisi

- **Doz**
  - %20 lik ILE den 1,5 mL/kg bolus, 0,25-0,50 mL/kg/dk infüzyon (500-1200 ml/gün)
- **Yan etki**
  - Arrest, DIC, Trombositopeni, lökopeni, renal yetmezlik, metabolik asidoz

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REVIEW

## Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration

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# Diğer tedavi alternatifleri

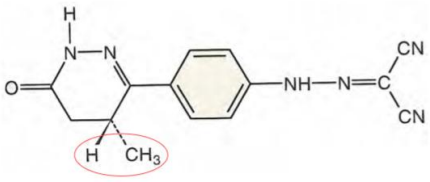
- Fosfodiestraz inhibitörleri
- Levosimendan
- Metilen mavisi
- L-carnitine

# Fosfodiestraz inhibitörleri

- cAMP yıkımını inhibe ederek hücre içi kalsiyum seviyelerini yükseltirler.
- Amrinon, milrinon ve enoksimon gibi fosfodiesteraz inhibitörlerinin kan basıncını iyileştirmede etkisi olduğu ile bildirilmiştir.
- Doz:
  - İnamrinon: 5 mcgr/kg/dk
  - Milrinon: 0,5 mcgr/kg/dk
  - Enoksimom: 0,75 mcgr/kg/dk


- Goenen M, Col J, Compere A, Bonte J: Treatment of severe verapamil poisoning with combined amrinone-isoproterenol therapy. *Am J Cardiol* 58: 1142,1986.
- Koury SI, Stone CK, Thomas SH: Amrinone as an antidote in experimental verapamil overdose. *Acad Emerg Med* 3: 762, 1996.
- Sandroni C, Cavallaro F, Addario C, et al: Successful treatment with enoximone for severe poisoning with atenolol and verapamil: a case report. *Acta Anaesthesiol Scand* 48: 790, 2004.
- Wood DM, Wright KD, Jones AL, Dargan PI: Metaraminol (Aramine) in the management of a significant amlodipine overdose. *Hum Exp Toxicol* 24: 377, 2005.

# Levosimendan




(-)-(R)-[[4-(1,4,5,6-tetrahidro-4-metil-6-okso-3-piridazinil)fenil]hidrazono]propanedinitril

- Yeni nesil inotropik ajanlardandır.
- Akut dekompanse kalp yetmezliği kılavuzundadır.
- Kalsiyum duyarlılaştırıcı (troponin C'ye bağlanarak miyofibrilleri Ca+2 a karşı daha duyarlı yapar) ve ATP duyarlı potasyum kanallarını açar → vasodilatasyon.
- Yan etki: VES, AF, Sinüs taşikardisi.

Levosimendan

# Metilen mavisi

- Dirençli hipotansiyon ve septik/anafilaktik şok durumunda 15 yıldır kullanılıyor
  - NO yolağında “Guanilil siklaz inhibisyonu”
- KKB, BB ve metformin aşırı alımı
- Doz: 1 mg/kg bolus, 0.1 mg/kg/saat infüzyon, OAB>70 mmHg olacak şekilde

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REVIEW

## A systematic analysis of methylene blue for drug-induced shock

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TOXICOLOGY/CASE REPORT

# Methylene Blue in the Treatment of Refractory Shock From an Amlodipine Overdose

David H. Jang, MD, Lewis S. Nelson, MD, Robert S. Hoffman, MD

*From New York University School of Medicine, Bellevue Hospital Center and New York University Langone Medical Center, New York, NY, and New York City Poison Control Center, New York, NY.*

Amlodipine is a potent vasodilator with a long half-life and delayed onset of action that is particularly concerning after an overdose. Vasodilation occurs through stimulation of nitric oxide release with increased cyclic guanosine monophosphate (cGMP) production. Methylene blue inhibits guanylate cyclase. This enzyme is responsible for the production of cGMP. Methylene blue also has the ability to scavenge nitric oxide, as well as inhibit nitric oxide synthase. We report the use of methylene blue for refractory shock in a patient with amlodipine toxicity. [Ann Emerg Med. 2011;58:565-567.]

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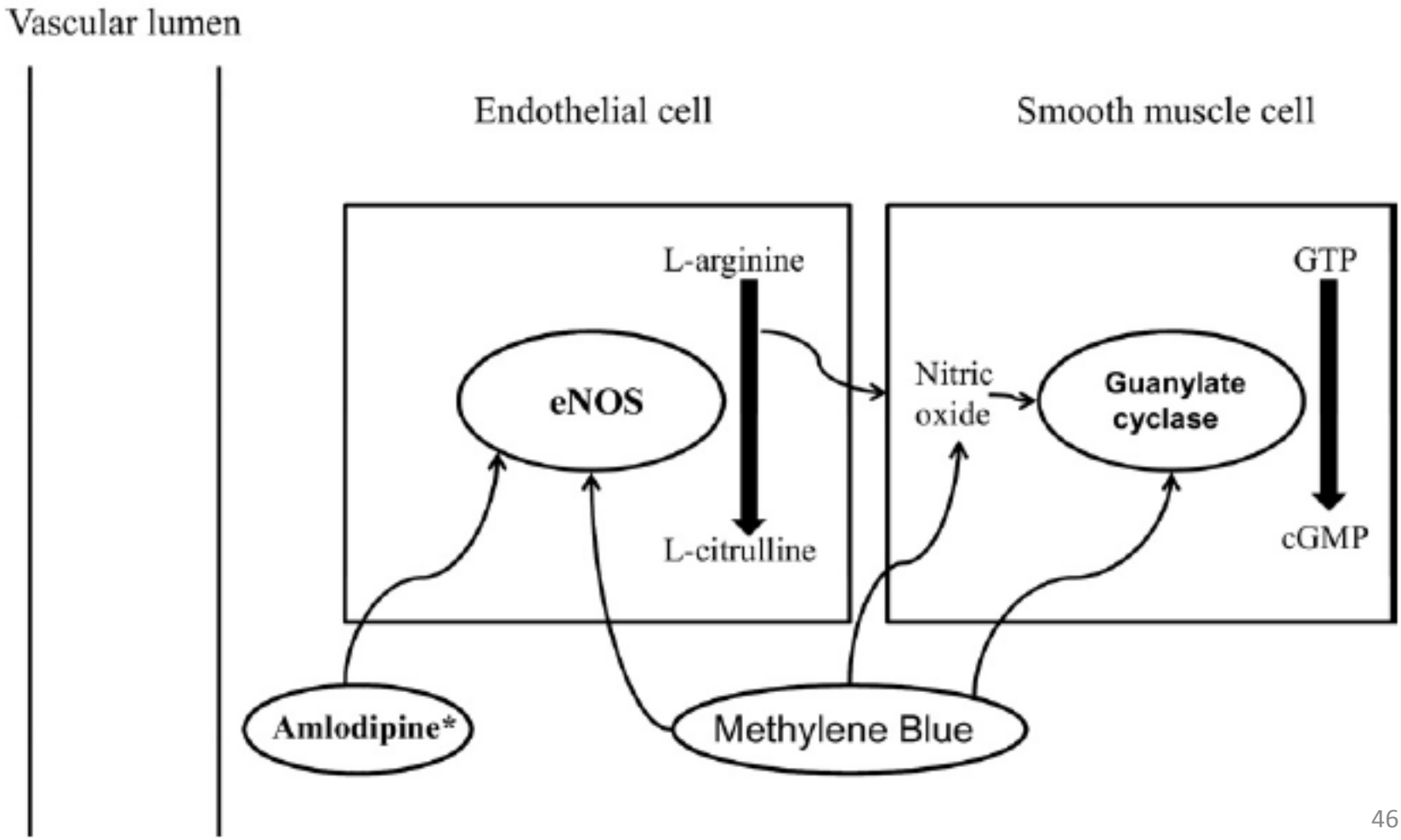
doi:10.1016/j.annemergmed.2011.02.025



# L-carnitine

- KKB zehirlenmesinde kardiyak mekanizma serbest yağ asitlerinden karbonhidratlara dönmektedir.
- L-carnitin bunu tekrar yağ asitlerine döndürmektedir.
- Etki: OAB ve surveyi arttırmaktadır.
- Doz: 6 gr IV bolus, her 4 saatte 1 gr IV

J. Med. Toxicol. (2013) 9:266–269
DOI 10.1007/s13181-013-0301-3

TOXICOLOGY OBSERVATION

# L-Carnitine for the Treatment of a Calcium Channel Blocker and Metformin Poisoning

Maude St-Onge · Ian Ajmo · Diane Poirier · Martin Laliberté

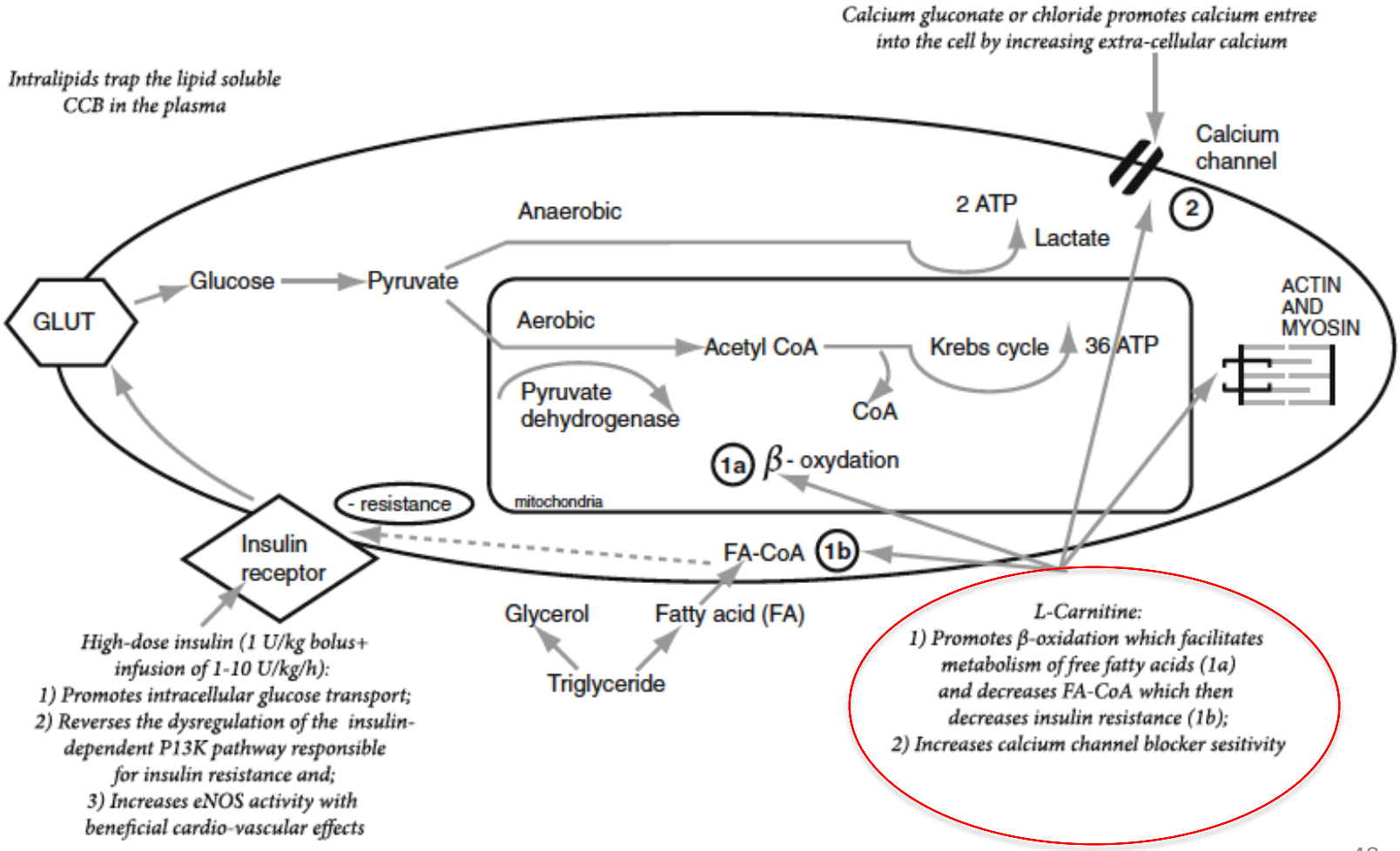
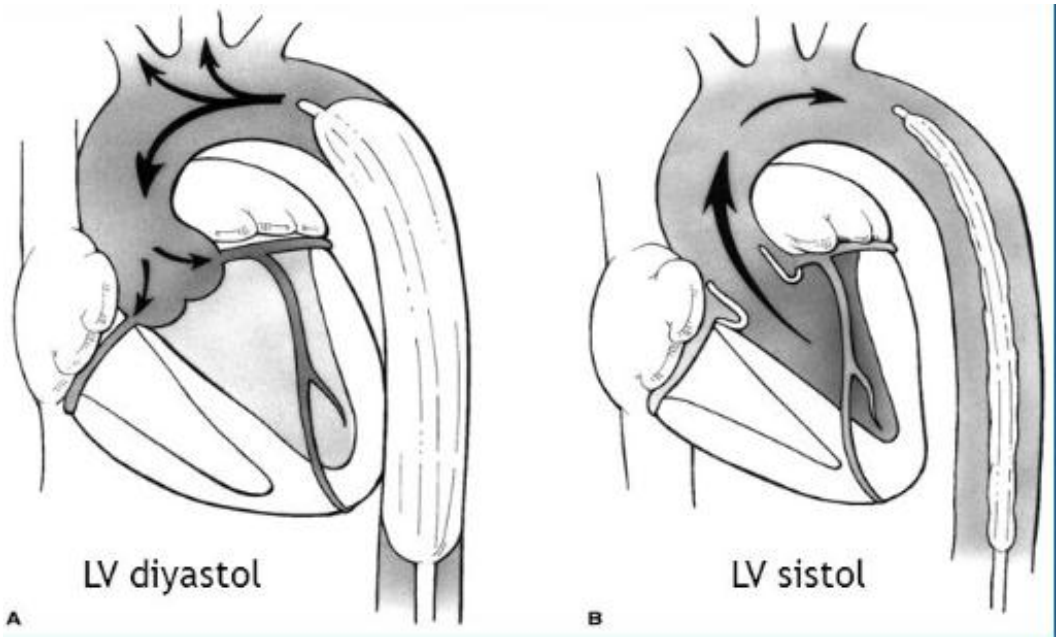



**Fig. 2** Mechanism of action of antidotes used in CCB poisoning

# Ek Hemodinamik Destek Tedavisi

- Ekstrakorporeal dolaşım (ECMO)
- Aortik balon pompası



# ECMO

- Yaşamı tehdit eden, hemodinamik dengesizliği olan ciddi ilaç zehirlenmelerinde volüm replasmanı, inotrop desteği, vazokonstriktörler ve bazende intra-aortik balon pompasına rağmen şokun devam ettiği durumlarda **VA-ECMO** kullanılabilir.
- Özellikle Acil Servis ve YBÜ'lerinde;
  - KKB
  - BB
  - Trisiklik antidepresanlar

Emergency extracorporeal life support **(ECLS)** in refractory shock or cardiac arrest following a drug overdose.

Massetti M, Bruno P, Babatasi G, Neri E, Khayat A: Cardiopulmonary bypass and severe drug intoxication. *J Thorac Cardiovasc Surg* 2000, 120:424-425.

*Clinical Toxicology* (2013), **51**, 385–393
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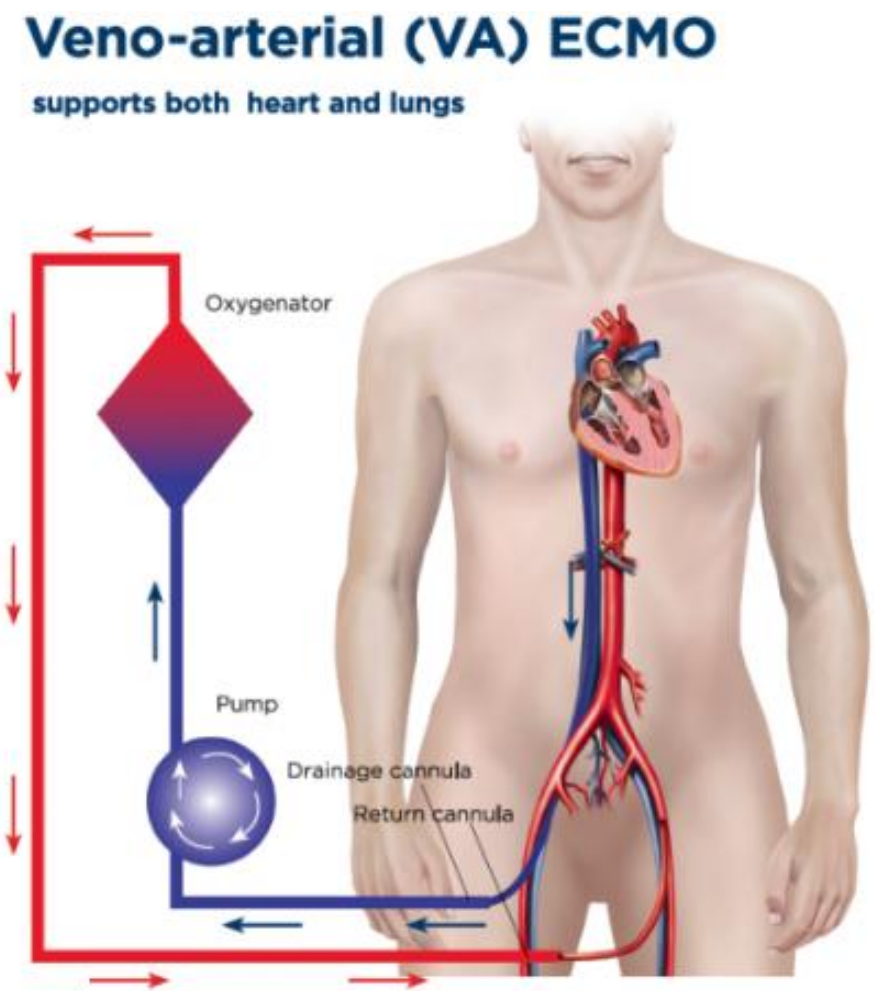
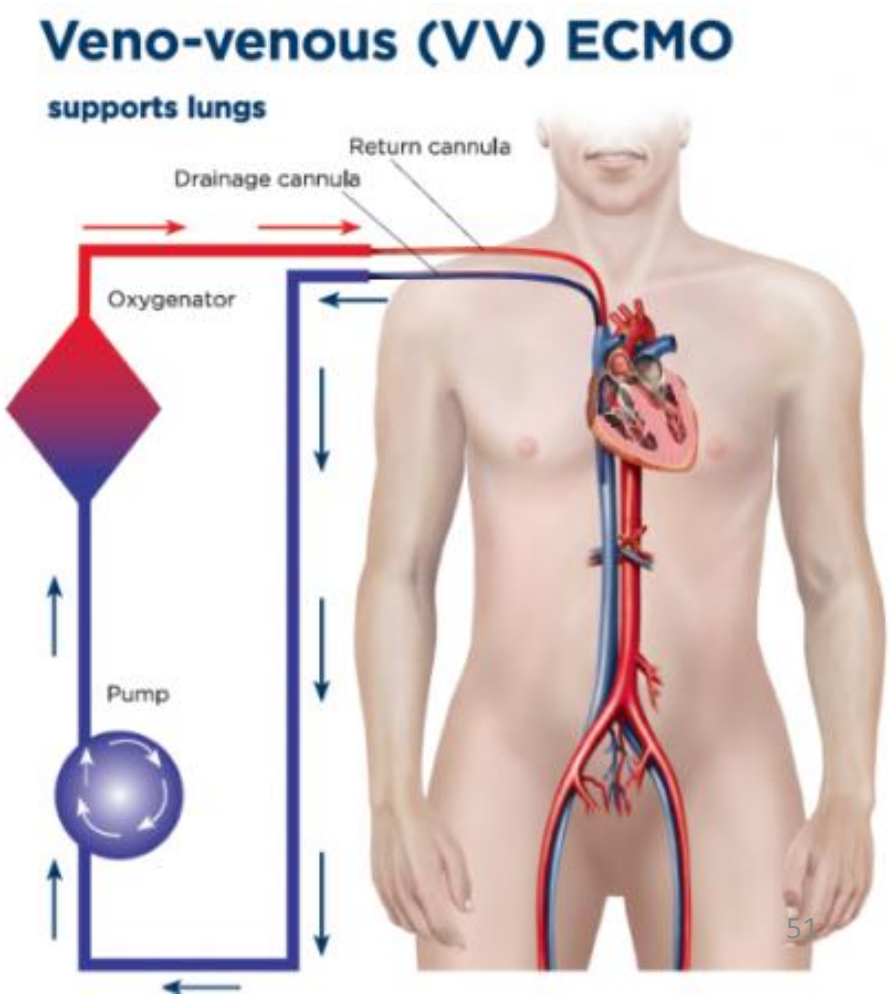
DOI: 10.3109/15563650.2013.800876

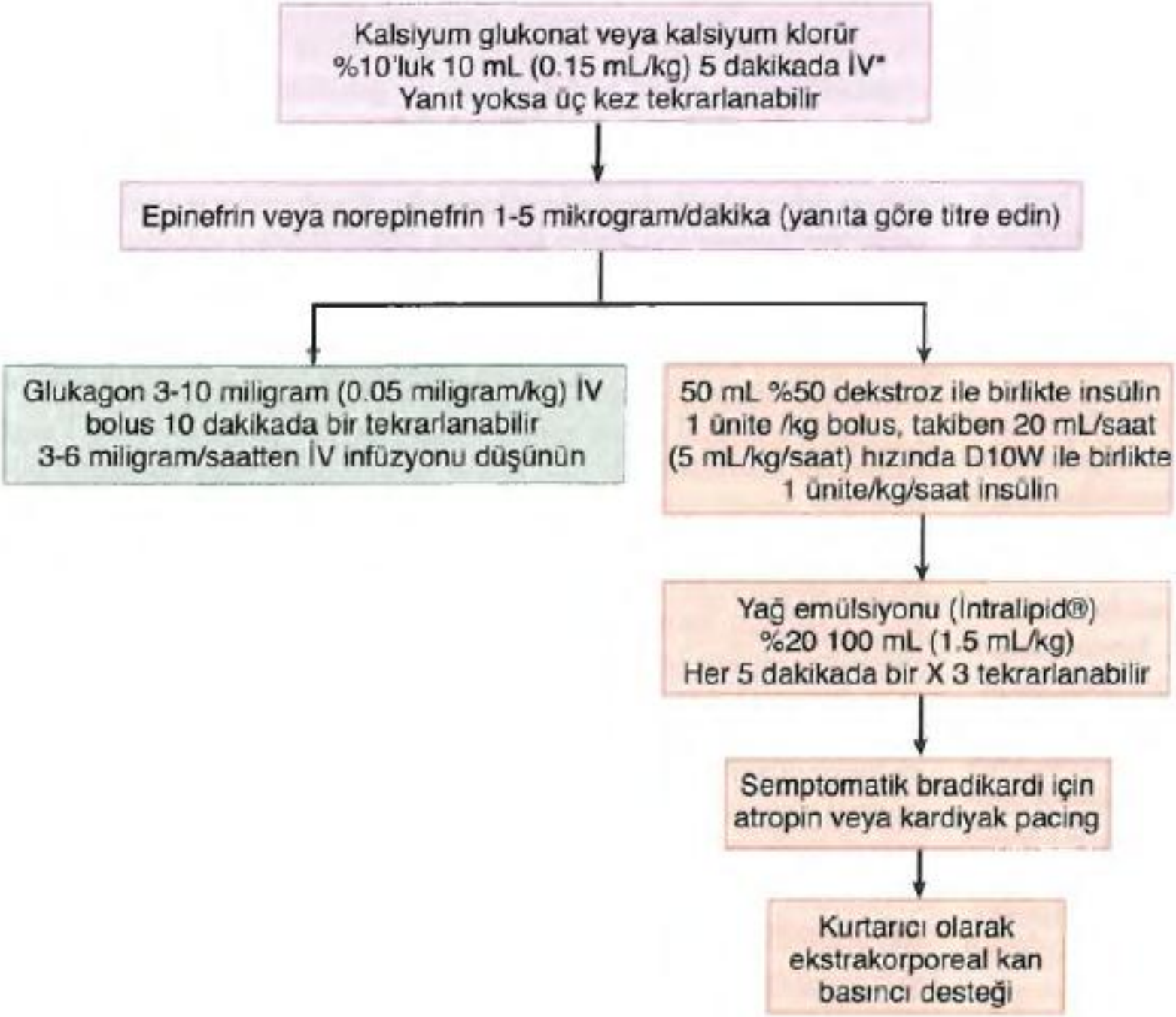
REVIEW ARTICLE

# Extracorporeal membrane oxygenation in the treatment of poisoned patients

D. W. DE LANGE[1,2,3], M. A. SIKMA[1,2], and J. MEULENBELT[1,2,4]




Kalsiyum glukonat veya kalsiyum klorür
%10'luk 10 mL (0.15 mL/kg) 5 dakikada İV*
Yanıt yoksa üç kez tekrarlanabilir
Epinefrin veya norepinefrin 1-5 mikrogram/dakika (yanıta göre titre edin)
Glukagon 3-10 miligram (0.05 miligram/kg) İV bolus 10 dakikada bir tekrarlanabilir
3-6 miligram/saatten İV infüzyonu düşünün
50 mL %50 dekstroz ile birlikte insülin 1 ünite /kg bolus, takiben 20 mL/saat (5 mL/kg/saat) hızında D10W ile birlikte 1 ünite/kg/saat insülin
Yağ emülsiyonu (İntralipid®)
%20 100 mL (1.5 mL/kg)
Her 5 dakikada bir X 3 tekrarlanabilir
Semptomatik bradikardi için atropin veya kardiyak pacing
Kurtarıcı olarak ekstrakorporeal kan basıncı desteği

# Takip

- Genellikle uzun salınımlı ilaç almamış olanlar **6 saat** içerisinde toksisite belirtileri gösterirler.
  - Dolayısıyla bu süre içerisinde yaşamsal bulguları normal olan ve başka bir belirtisi olmayan hastalar uygun psikiyatrik değerlendirme yapıldıktan sonra taburcu edilebilirler.
- Kural olarak ise; potansiyel toksik dozlarda uzamış-salınımlı bir ilaç almış olan hastalar **12-24 saat** gözlem altında tutulmalıdır.
- Diğer hastalar ise YBÜ'ne yatırılmalıdır.

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