Antianginás szerek & Kálcium antagonisták

Megyeri Attila

2020.09.22.

Myocardialis ischaemia

- egyensúly felborul: (O_2) **ellátás**(kínálat)<**igény**(kereslet)
  - szöveti hypoxia → ↑ metabolitok → **fájdalom**
    - angina pectoris *(angere = szorítani, pectus = mellkas)*
    - de van: “silent” ischemia is
- angina típusai
  - effort (klasszikus, stabil, terhelésre jelentkező)
  - vazospasztikus (variant, Prinzmetal – lokális érgörcs)
  - instabil – (plakk ruptura, részlegesen elzáró labilils trombus)

háttérben: atherosclerosis / coronaria betegség

Myocardialis ischaemia

- korrekció lehetőségei
  - **↓ igény** (kereslet)
    - ↓ szív munka
    - hatékonyabb metabolizmus (kevesebb O_2 per ATP)
  - **↑ ellátás** (kínálat)
    - coronaria dilatatio

Kereslet

(a myocardialis **oxigén igény** meghatározói)

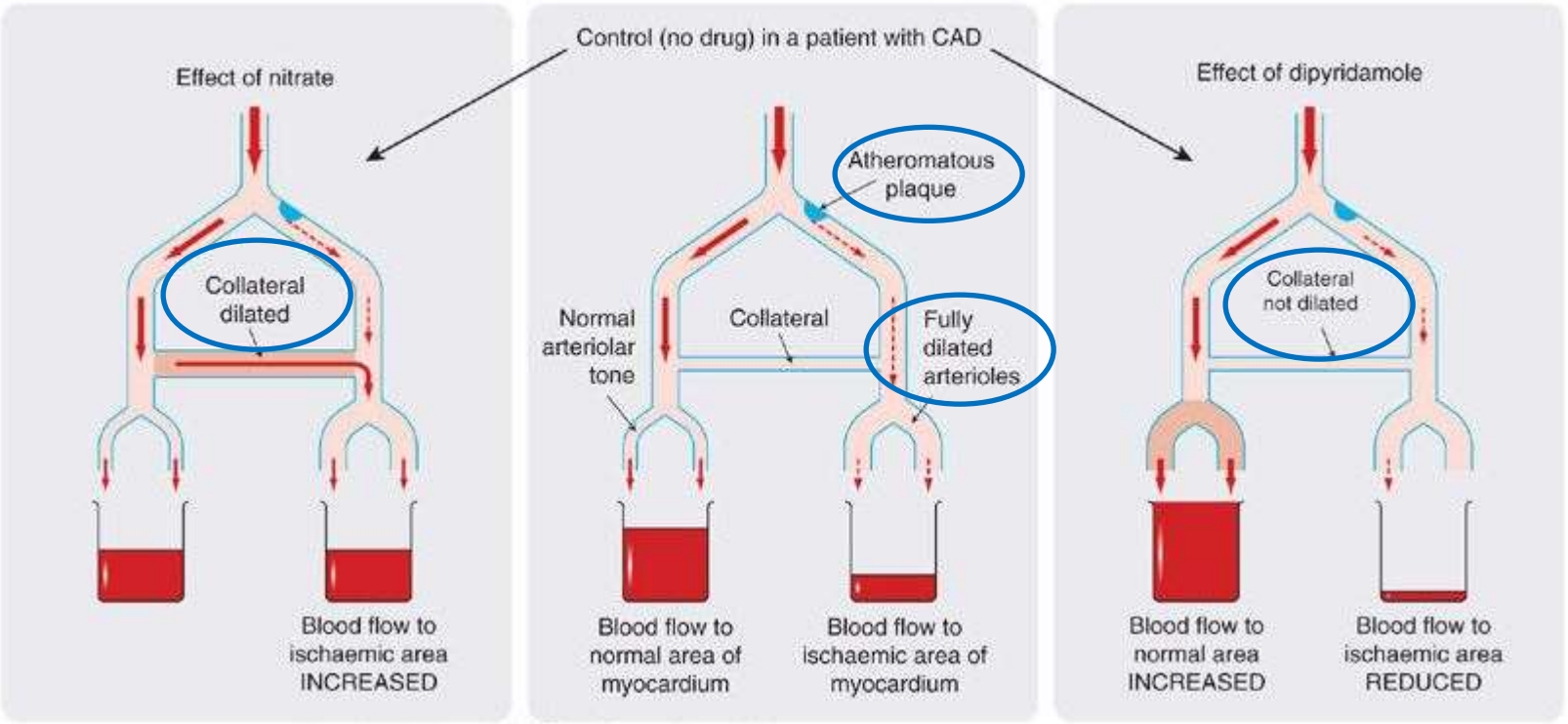
- szívfrekvencia
- kontraktilitás
- falfeszülés ← arteriás nyomás (systoles), perifériás vénás tónus (diastoles)
  - intraventricularis nyomás
  - kamraátmérő (térfogat)
  - falvastagság

Kínálat

(a coronaria áramlás & a myocardialis **oxigén ellátás** meghatározói)

- coronaria vascularis rezisztencia (fordított arány)
  - coronaria rezisztenciát befolyásoló tényezők
    - metabolitok
    - vegetatív aktivitás
    - gyógyszerek
    - endothelium károsodás
      - sérült endothelium→coronaria nem dilatál (ld coronaria ”steal”)
- perfusios nyomás (aorta diastoles nyomása)
- diastole tartama

Coronary steal



no steal control steal

- a nitrátok angina esetén jól használhatók
  - nem csak a koronáriákra hatnak
- dipyridamole angina esetén nem jó
  - diagnosztikus stressz tesztként használható

Gyógyszeres kezelés angina pectorisban?

- sok beteg **nem** alkalmas
  - revascularizációra – PCI („percutaneous coronary intervention”)
  - „coronary artery bypass graft surgery” (CABG)
- jelentős hányadban nem teljes a revascularizáció PCI vagy CABG után
- ilyenkor: **gyógyszeres terápia**
  - hagyományos antianginás szerek
  - újabb antianginás szerek (általában refrakter anginára)

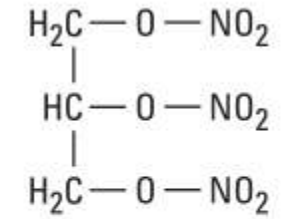
Antianginás szerek csoportjai

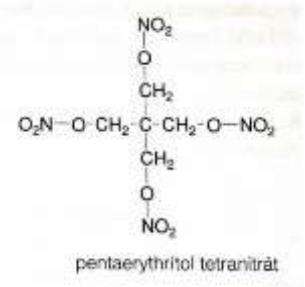
- szerves **nitrátok** (pl. nitroglycerin)
  - elsősorban akut kezelésre de prophylaxisra is
- **calcium csatorna blokkolók** (pl. nifedipine)
  - prophylaxisra
  - dihydropyridinek és nem-dihydropyridinek
- **β blokkolók**
  - prophylaxisra
- **újabb antianginás szerek**
  - *ranolazine* – ic. Ca ↓ → ↓ kontraktilitás
  - *trimetazidine* – hatékonyabb O_2 felhasználás
  - *ivabradine* – ↓ szívfrekvencia

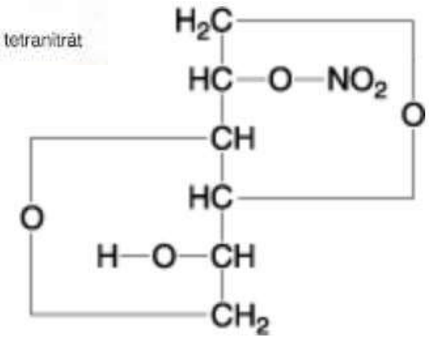
elsődleges: ↓ O_2 igény: ↓ frekvencia / kontraktilitás / kamra fal feszülés
járulékosan: ↑ O_2 ellátás: coronaria dilatáció (variáns anginában elsődleges)

Nitrátok

- **nitroglicerin** = glyceryl trinitrát (GTN)
  - a prototípus
  - illékony, adsorptio műanyagokhoz - spray
- amilnitrit
  - illékony, belégzésre, elavult
- isosorbid dinitrát (ISDN)
  - nitroglicerinnél lassabb felszívódás, hasonló metabolizmus
- *isosorbid-5-mononitrát (ISMN)*
  - jó orális biol. hozzáf., lassú hatás, akutan nem
- pentaerythritol tetranitrát
  - tartós hatás
- nicorandil
  - kombinált: NO felszabadulás + K^+ csatorna nyitás
- *molsidomine*
  - profarmakon, akut kezelésre nem
  - spontán NO felszabadulás / tolerancia ritkább ?
- nitroprusside
  - parenteralis, hypertensiv krízis (nem angina), spontán NO felszab.
  - vénás és artériás dilatator is, fényérzékeny, cianid mérgezés, rövid hatástartam






isosorbide mononitrate

Nitrátok hatásmechanizmusa

- **NO felszab.** → guanilát cikláz↑ → cGMP↑ → PKG↑ → MLC foszforiláció↓ → **simaizom relaxáció**
  - enzimatikus
    - GTN: mitochondrial aldehyde dehydrogenase (ALDH2) + mások?
  - "direkt" (nem-enzimatikus)
    - pl. molsidomine
- elsősorban **venodilatáció** (túladagolás veszélyes)
  - + epicardialis coronariák + atherosclerotic stenosis + collateralis erek (nincs "coronary steal")
- egyéb simaizmok
  - bronchusok, gastroint., genitourin. – klinikai haszon ?
- *thrombocyta aggregáció* gátlás (mérsékelt)

Pharmacokinetics of nitrates

- nitroglycerine (GTN)
  - for acute use:
    - **sublingual** tablet, **spray**
    - avoids first pass effect
    - quick onset (peak ~ 4 min)
    - short duration (30 min)
      - high dose is not possible
  - for chronic use (longer duration)
    - larger oral doses
    - transdermal patches
    - buccal slow release
- isosorbide mononitrate
  - oral F=100%
  - slow onset → no acute use

Nitrátok terápiás indikációi

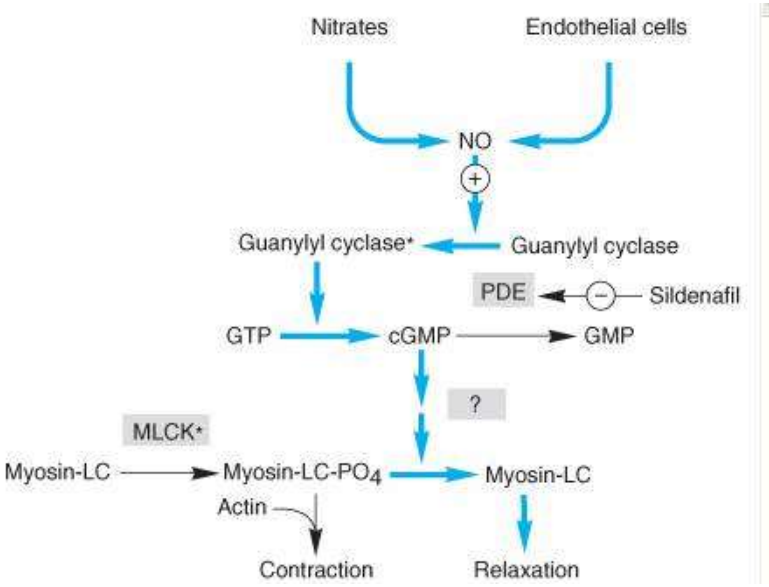
- bármely típusú angina
  - effort – fő: ↓ vénás vissza → ↓ intracardialis térfogat → ↓ O_2 fogy.
  - instabil - ? – coronaria dil / ↓ O_2 fogy / thrombocyta ↓
  - Prinzmetal / variant – coronaria relaxáció
- kombinációban
  - β-blokkolókkal vagy Ca csatorna blokkolókkal
- akut kezelésre és profilaxisra is
- tartós alkalmazás ?
  - tolerancia ? / mortalitás ?

Nitráttolerancia, mellékhatások, interakciók

- **tolerancia**
  - mechanizmus ?
    - neurohumoralis aktiváció, SH depléció, szabadgyökök, a mitochondrialis aldehid-dehidrogenáz inaktivációja ...
  - csökkentésre: **szakaszos adagolás**
- mellékhatások – **dózis**függő!
  - lüktető fejfájás / arckipirulás
  - orthostaticus hypotonia
  - reflex tachycardia
  - methaemoglobinaemia
    - ld. nitrát → nitrit – csecsemőkben
    - cianid mérgezésben használták
  - ↑ intracranialis nyomás (túladagoláskor) - kontraindikáció
- interakciók
  - sildenafil (Viagra®)
  - antihipertenziv szerek

Interaction of nitrates with PDE5 inhibitors

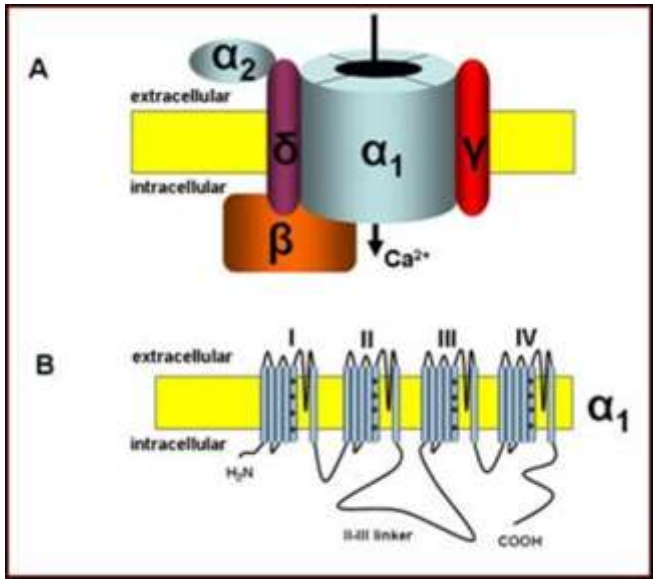
- risk factors for erectile dysfunction ≈ coronary artery disease
- PDE5 inhibitors: **sildenafil** (Viagra), **tadalafil** (Cialis), **vardenafil** (Levitra)
- profound cGMP ↑ → severely reduced BP



indications of PDE5 inhibitors: **erectile dysfunction, pulmonary hypertension**

Ca^{2+} channel blockers

- **voltage activated** Ca^{2+} channels
  - several types: **L,** *T*, N, P/Q, R
    - **currently** used drugs are **L-type** Ca^{2+} channel blockers (mostly)
  - **depolarization** → opening → EC Ca^{2+} entry → contraction
    - although different in smooth muscle and heart



Ca^{2+} channel blockers

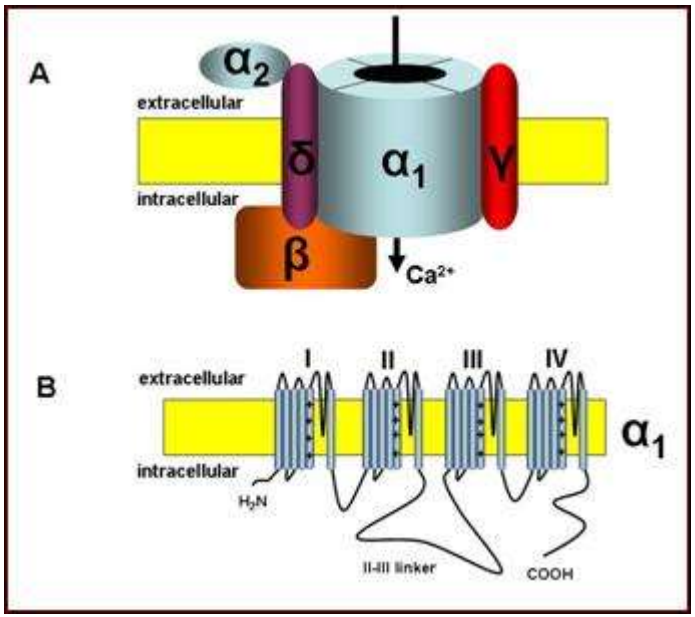
tissue selectivity

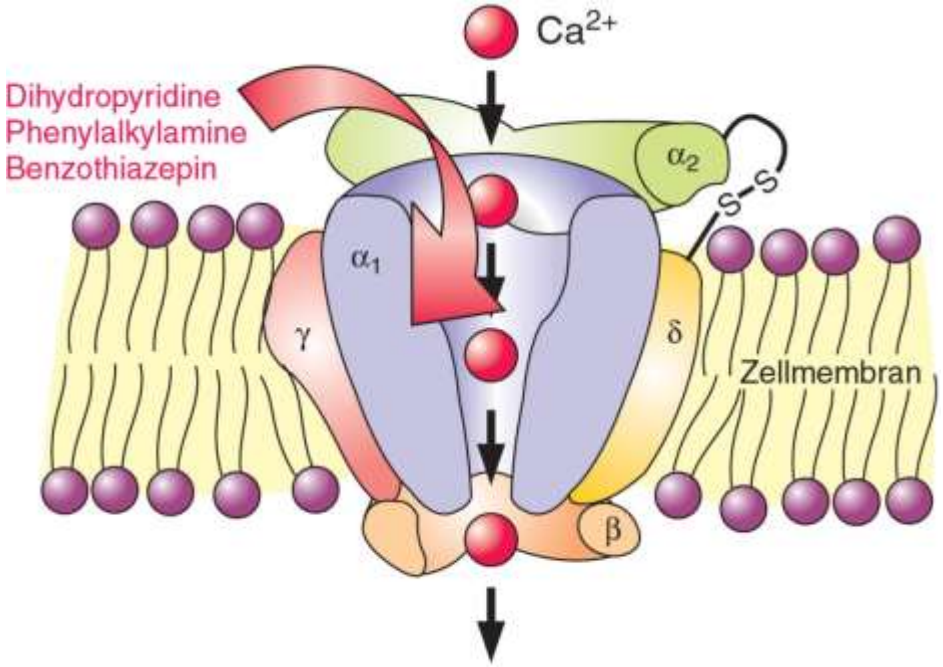
- **vascular smooth muscle relaxation**
  - primarily dihydropyridines: **nifedipine, amlodipine ...**
  - **predominantly arterial → blood pressure and TPR ↓**
  - coronaries → variant angina
  - vascular bed selectivity: e.g. nimodipine – cerebral arteries (evidence?)
- **heart: negative inotrop**, chronotrop, dromotrop
  - cardiac myocytes, SA, AV nodal cells
  - primarily: **verapamil** / **diltiazem**
- **other tissues**: no / less effect (relative)
  - skeletal muscle, bronchi, neural tissue / gastroint., genitourin.

drug	vasodilation	contractility ↓	automaticity ↓	conduction ↓
verapamil	4	4	5	5
diltiazem	3	2	5	4
nifedipine	5	1	1	0

relative effects: 0 = no effect, 5 = prominent effect

Mechanism of action / basis of selectivity





- all bind to α1 – but at **different sites**
- reduced Ca^{2+} influx → relax. / neg. inotropy / ↓ SA / ↓ AV
- verapamil – **use dependent** blockade / **↓ rate of recovery** of the slow Ca^{2+} channel in SA and AV nodes → cardiac eff.

Mechanism of action

- smooth muscle relaxation
  - **vascular**
    - **predominantly arterial → blood pressure and TPR ↓**
    - coronaries → variant angina
    - different vascular selectivity: verapamil ↔ nifedipine
    - vascular bed selectivity: e.g. nimodipine
  - bronchiolar, GI, uterine
- cardiac muscle contractility ↓
- SA node pacemaker rate ↓
- AV nodal conduction rate ↓

verapamil (diltiazem)

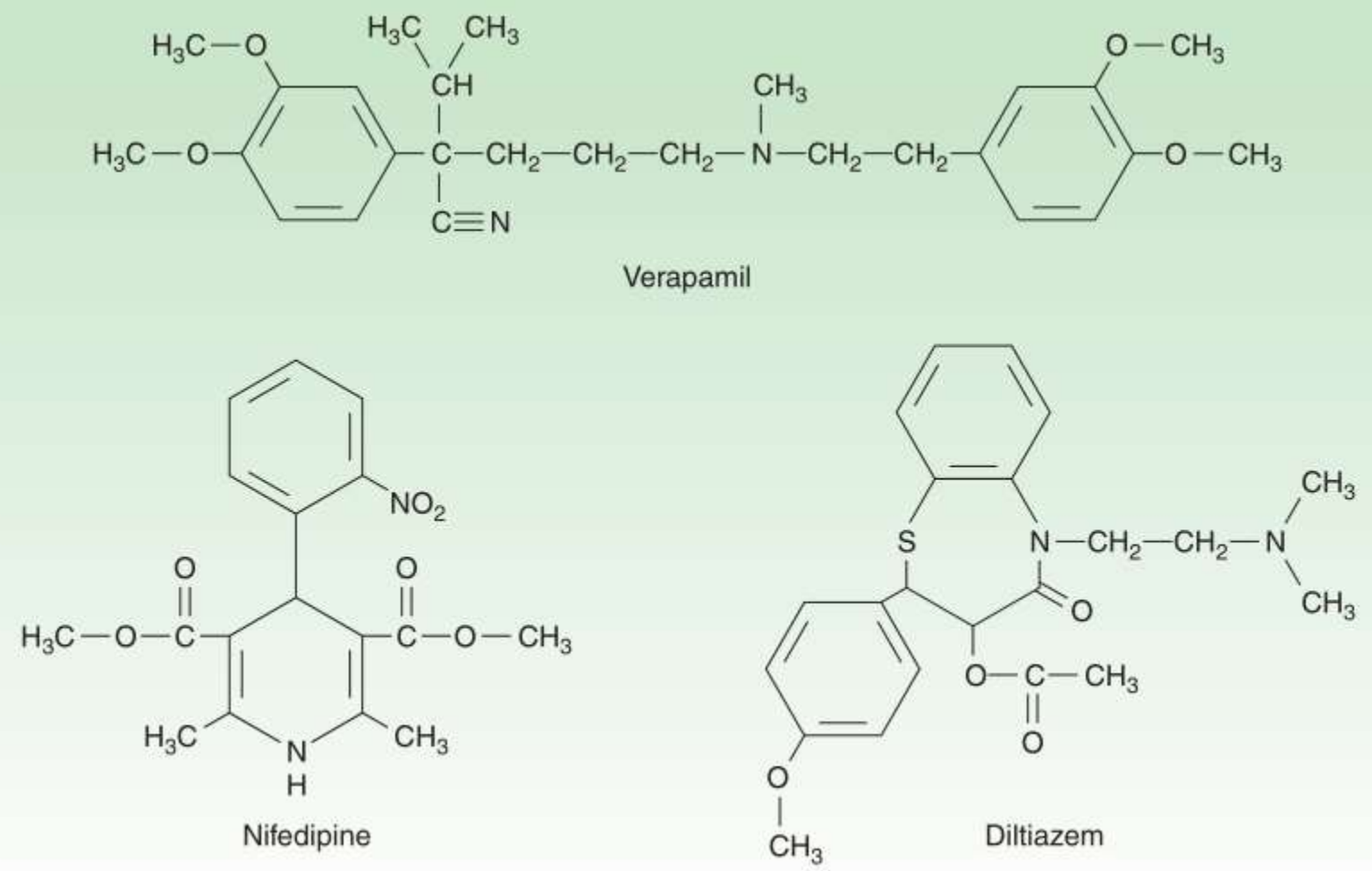
Classification

- chemical
  - phenylalkilamine: verapamil
  - benzothiazepine: diltiazem
  - dihydropyridines (DHP): nifedipine, amlodipine ...
- functional
  - heart active (verapamil / diltiazem) – **no tachycardia**
  - vessel active (DHP) – tachycardia (baroreflex)

drug	vasodilation	contractility ↓	automaticity ↓	conduction ↓
verapamil	4	4	5	5
diltiazem	3	2	5	4
nifedipine	5	1	1	0

relative effects: 0 = no effect, 5 = prominent effect

Chemical structures



Pharmacokinetics

- Absorption
  - good oral abs. + high first pass hepatic metabolism →↓ oral bioavail.
  - iv.: *verapamil, nifedipine, nimodipine*, nicardipine
  - bioavail.↑: grapefruit juice, cirrhosis, saturation of metabol.
  - fast absorption → quick onset → high C_{max}
    - deleterious: more pronounced baroreceptor reflex activation
    - except for e.g. amlodipine, lacidipine, sustained release nifedipine
- Distribution
  - high plasma protein binding
- Elimination
  - variable half-lives (1.3-64 h)
    - longer half life is more desirable
    - sustained-release forms (e.g. nifedipine)
  - extensive liver metabolism
    - inactive or weakly active metabolites
    - *verapamil, diltiazem*: CYP3A4 / P-gp blockade → drug interactions

Duration of action of DHPs

- short
  - *nifedipine**, *nimodipine*, nicardipine
- intermediate
  - *felodipine*, *nisoldipine*, nitrendipine, isradipine
- long
  - *amlodipine, lacidipine*

*but see sustained release formulations

Clinical use of Ca^{2+} channel blockers

- **antihypertensive**
- **antianginal**
- antiarrhythmic (*verapamil, diltiazem*)
- other
  - hypertrophic cardiomyopathy
  - migraine
  - Raynaud's phenomenon
  - preterm labor
  - post subarachnoid hemorrhage *(nimodipine)*

Ca^{2+} channel blockers in angina

- peripheral vasodilation
  - predominantly arterial
  - blood pressure and TPR ↓ → ↓ afterload → ↓ wall stress (systolic) → ↓ O_2 demand
- coronary dilation
  - important primarily in variant angina
  - most effective prophylaxis in variant angina
- other heart effects (non-dihydropyridines)
  - ↓ contractility / ↓ frequency

Other indications of Ca^{2+} channel blockers

- supraventricular tachyarrhythmias - verapamil
  - paroxysmal supraventricular tachycardia (PSVT)
  - atrial fibrillation / flutter (except +WPW)
- hypertension
  - chronic: no short acting oral dihydropyridines
  - acute: i.v. clevidipine, nicardipine, *verapamil* / oral *nifedipine*

Other indications of Ca^{2+} channel blockers

- hypertrophic cardiomyopathy
  - verapamil – improved LV outflow obstruction
- migraine
  - for prophylaxis only
- Raynaud's phenomenon
  - *nifedipine, felodipine, diltiazem*
- preterm labor
  - not primary
- post subarachnoid hemorrhage
  - *nimodipine*
  - prevent cerebral vasospasm

Adverse effects

- arteries
  - headache, flushing, dizziness
    - immediate release oral nifedipine
  - peripheral edema (ankle edema)
    - increased hydrostatic pressure
- other
  - gastroesophageal reflux
  - constipation – verapamil
- heart
  - worsening of ischemia / angina
    - excessive hypotension / “coronary steal” / ↑ O_2 demand
  - bradycardia, transient asystole, exacerbation of heart failure
    - iv. verapamil + SA / AV disease or β-blocker use

Specific dihydropyridines

- ***nifedipine***
  - prototype, short acting, acute use or sustained rel.
- *amlodipine*
  - delayed onset, long acting
- *felodipine*
  - intermediate duration, even greater vascular specificity
- *lacidipine*
  - lipophilic, slow onset, long duration, vascular selectivity, antioxidant activity
- *nimodipine*
  - cerebral vessel specific
- isradipine
  - typical peripheral vasodilation, negative chronotrop but little effect on AV conduction, no rise in heart rate
- clevidipine
  - newer, iv only, quick onset, short duration, artery specific
- nicardipine
  - oral and iv., coronary selective ?, good for cerebral vasospasms ?

β blockers in angina

- not vasodilators (with a few exceptions)
- useful effects in angina
  - ↓ *heart rate* / ↓ contractility / ↓ blood pressure
    - ↓ O_2 requirement
    - ↑ *diastolic perfusion time* → ↑ *coronary perfusion*
- clinical use
  - effort angina (silent!)
    - in stable angina clinical trials: β blockers > Ca blockers
  - after myocardial infarction
  - but **do not use in vasospastic angina**

β blockers

- undesirable effects in angina
  - ↑ end-diastolic volume / ↑ ejection time
    - might ↑ O_2 requirement
    - to prevent: combination with nitrates

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	*Reflex*[1] *increase*	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	*Increase*	None or decrease
Contractility	*Reflex*[1] *increase*	Decrease	None
Ejection time	Decrease[1]	*Increase*	None

[1]Baroreceptor reflex.

Note: Undesirable effects are shown in italics.

Adverse effects of β-receptor blockers

- bradycardia
- bronchoconstriction (in asthma)
- cardiac decompensation
  - see interaction with verapamil
- cold hands and feet
- sedation, vivid dreams, depression
- VLDL ↑, HDL/LDL ratio ↓
- hypoglycemia ? – IDDM
- worsening of peripheral vascular disease
- β-receptor up-regulation
  - gradual dose tapering

Ranolazine

- relatively new drug in angina (Ranexa®)
- reduces a late sodium current (I_{Na})
  - Na-Ca exchanger Na entry ↓ → ic. Ca ↓ → contractility → ↓ O_2 demand
- for chronic treatment in **stable angina**
  - primarily in those **who are unresponsive to other**
- antiarrhythmic properties
- potential PK drug interactions
  - liver metabolism (CYP3A4, CYP2D6) / P-gp
- may prolong QT interval

Trimetazidine

- a metabolic modulator
  - partially ↓ fatty acid oxidation pathway (pFOX inhibitor)
    - fatty acid oxidation requires more O_2 per ATP
    - inhibition seems to improve metabolic status
- approved in Europe (but not in US)
- no significant effects on heart rate
- Parkinson's disease risk ↑ (EMA, 2012)
  - second line

Ivabradine

- a bradycardic
  - relatively selectively blocks I_f Na channel (funny current)
  - ↓ heart rate
    - blocks hyperpolarization-activated Na ch in SA node
  - no other hemodynamic effects
- reduces the number of anginal attacks
  - not for acute treatment
- free of GI and bronchial effects

Drugs in unstable angina & acute coronary syndromes

- antiplatelet therapy
  - combination of aspirin and clopidogrel
- iv. heparin or sc. LMWH
- if PCI with stenting
  - glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide)
- nitroglycerin
- β-blockers
- lipid-lowering
- ACE-inhibitor