Les anti-arythmiques

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History of antiarrhythmic drug development

- 1910 – 1920 Quinidine
- 1950 – 1970 Lidocaine, procainamide, diphenylhydantoin, disopyramide
- 1960 – 1970 mexiletine, tocainide
  beta blockers = propranolol, sotalol
  coronary vasodilators = verapamil, amiodarone
- 1970 – 1980 Pure fast Na^{++} channel blockers = encainide, flecainide

Antiarrhythmic activity of: Beta blockers
Sotalol
Verapamil
Amiodarone

Singh-Vaughan Williams classification

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Classification of antiarrhythmic mechanisms

Class I drugs delay fast sodium-mediated conduction	Class II beta blockers	Class III prolong repolarization	Class IV Ca^{++} blockers
• Ia – Delay conduction – Prolong repolarization • Disopyramide • Procainamide • Quinidine	♦ Acebutolol ♦ Carvedilol ♦ Esmolol ♦ Metoprolol ♦ Nadolol ♦ Propranolol ♦ Timolol ♦ Others	♦ Amiodarone ♦ Azimilide ♦ Bretylium ♦ Dofetilide ♦ Dronedarone ♦ Ibutilide ♦ Sotalol ♦ Tedisamil	♦ Diltiazem ♦ Verapamil
• Ib – Depress phase 0 in abnormal tissue – Shorten repolarization or little effect • Mexiletine • Tocainide			
• Ic – Markedly slow conduction – Slight effect on repolarization • Flecainide • Propafenone			

Source B.M. Singh

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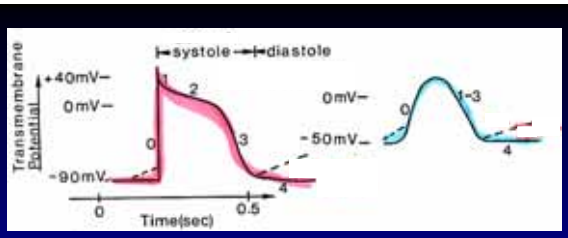

« Tissu Rapide »
Fast Channel Tissue

Classes I et III

« Tissu Lent »
Slow Channel Tissue

Classes II et IV

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Classes de Médicaments Antiarythmiques

- Class Ia
  - Quinidine
  - Procainamide
  - Disopyramide
- Class Ic
  - Flecainide
  - Propafenone
- Class III
  - Sotalol
  - Dofetilide
  - Azimilide
  - Ibutilide
- Amiodarone

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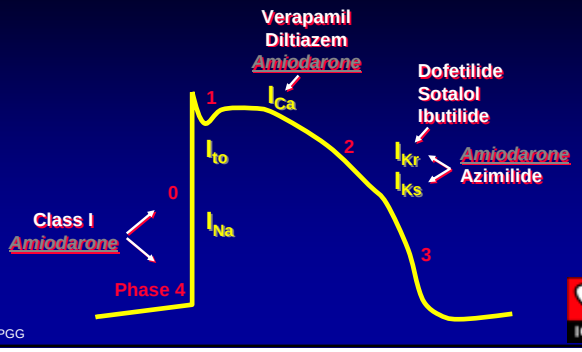
Effets des Anti-Arythmiques



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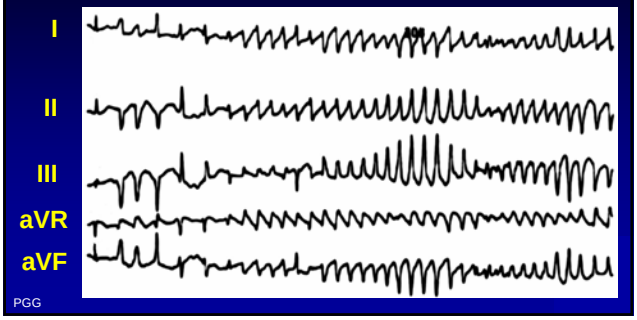
Torsades de Pointes



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Pharmacology of anti-arrhythmic medications

	Positives	Negatives
Class Ia	• Demonstrated efficacy • Familiarity	• High incidence of side effects • Idiosyncratic QT prolongation - TDP (1-3%) • ↑ mortality
Class Ic	• Better tolerated than class Ia drugs	• Atrial flutter with 1:1 conduction • ↑ mortality in post-MI pts

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Pharmacology of anti-arrhythmic medications

	Positives	Negatives
Class III		
Sotalol	• AV nodal blocking effect	• ß-blocking adverse events – Bradycardia – Asthma • TDP
Amiodarone	• Probably more effective than other drugs • Low proarrhythmia risk • Once a day	• Non-cardiac adverse effects – Lung – Thyroid • Time to achieve efficacy

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Proarrhythmia
Major limitation of antiarrhythmic therapy

Class I (Na^{++} channel blockers)

- ↑↑ conduction slowing
  - – Large doses of class Ic drugs
  - – Monomorphic incessant VT
- Ischemic
  - – Sporadic
  - – CAST

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Proarrhythmia

Class III (K^{+} channel blockers)

- ↑ APD
- Acquired LQTS
- Early after-depolarization (EAD) from Purkinje fibers
- Bradycardia - hypokalemia
- With or without organic heart disease
  - – ↑ CHF
  - – ↑ LVH

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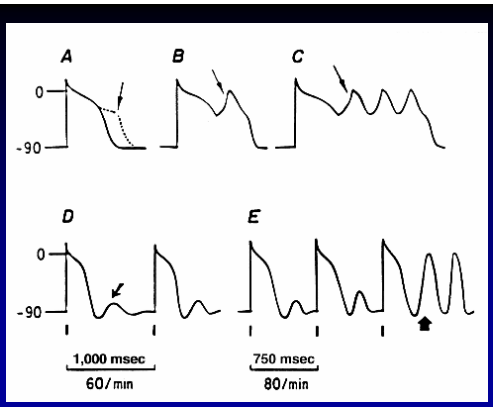

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Some Common Drugs That Can Prolong QT Intervals

- Class IA and III antiarrhythmics
- Tricyclic antidepressants
- Terfenadine, astemizole, and other antihistamines
- Erythromycin and other macrolides, trimethoprim/sulfa
- Probucol
- Ketoconazole and related antifungals
- Phenothiazines and several derivatives, including droperidol, haloperidol, risperidone
- Pentamidine
- Bepridil
- Sparfloxacin
- Cisapride
- Fluvoxamine, sertraline, and other SSRIs
- Nefazodone
- Zileuton

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Effets de l'Amiodarone

- Bloque cannaux sodiques, potassiques, calciques
- Bloque récepteurs béta et alpha adrénergiques
- prolonge durée du potentiel d`action, augmente périodes refractaires

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Pharmacologie de l'Amiodarone

- Absorption lente et variable !
- Biodisponibilité : 40%
- début de l'effet: 3 jours à 3 semaines
- très large volume de distribution
  - surtout dans les tissus adipeux
- protein bound (>98%)
- demi-vie: 20 à 60 jours, métabolisé par le foie

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Effets Secondaires d'Amiodarone

- Hab. réversibles et dose-dépendant
- **occulaires**:
  - microdépots
  - neuropathie optique (1.3%)
- **pulmonaires**:
  - dose et durée de la thérapie
  - 1-2%
- **thyroide**:
  - hypo : 5.9%
  - hyper : régions où iode peu consommé

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New class III antiarrhythmic agents

- **Specific I_{Kr} blocker**
  - Dofetilide
  - D-sotalol
  - Sematilide
  - E4031
  - MK 499
- **I_{Kr} and I_{Ks} blockers**
  - Azimilide
- **Multiple ion channels**
  - Ibutilide I_{Kr} blocker - I_{Na} activator
  - Tedisamil I_{To} - I_{Kr} blocker
  - Dronedarone I_{Na} - I_{Ca} - I_K blocker

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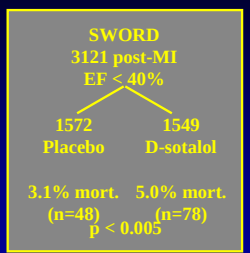
D-sotalol

- I_{Kr} blocker
- No beta blocker activity
- Extensive clinical evaluation
- Survival with oral d-sotalol (SWORD)
  - Withdrawn
- "The prophylactic use of a specific potassium-channel blocker may be associated with increased mortality…"



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New Class 3 Agents

Dofetilide

- Potent blocker of I_{kr}
- Effective in maintaning sinus rhythm
- Long-term use not associated with increased mortality in post-MI or CHF populations
- 3% incidence of torsades de pointes
- In-hospital initiation

Greenbaum et al. Circulation 1998
Torp-Pedersen et al. NEJM 1999

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Dofetilide

- Potent inhibitor of I_{Kr}
- 60% renal clearance
- Elimination half-life = 7-13 hrs
- Danish investigation on dofetilide (DIAMOND, MI/CHF)
- Neutral effect on mortality
- TDP 3.3% (<3 days)
- In-hosp initiation

DIAMOND -CHF
1518 pts
391 AF (26%)

	Conv to SR 1 month	Maintenance 1 year
Dofetilide	12%	80%
Placebo	1%	45%
p value	<0.001	<0.001

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Azimilide

- Class III (I_{Kr} and I_{Ks} blocker)
- Once-a-day
- Out-patient loading
- Clinical evaluation
  - AF/SVT
  - Post-MI (ALIVE)

	N	p	Median time to recurrence
Placebo	87		17 days
50 mg	99	0.37	22 days
100 mg	92	0.08	41 days
125 mg	89	0.002	130 days

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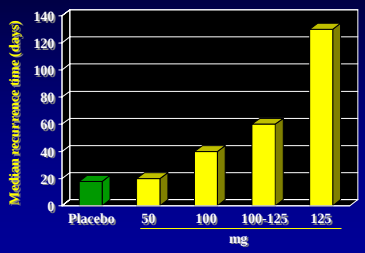
New Class 3 Agents

Efficacy of Azimilide



Pritchett et al. Circulation 1998; Abstract

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Dronedarone

- Class I, II, III, IV properties
- No iodine subgroup
- For AF-SVT-VT-sudden death?
- Possible year of approval = 2002?

Electrophysiologic effects of dronedarone vs amiodarone in rabbit heart

↑ RR, QT interval
↑ atrial and ventricular APD
↓ Vmax
"More potent than amiodarone"
Sun Circulation 1999

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Antiarrhythmic drugs for AF

Class IA	Class IC	Class III
Disopyramide	Flecainide	Amiodarone
Quinidine	Propafenone	Dofetilide
Procainamide		Sotalol
		Azimilide*
		Dronedarone*
		Trecetilide*

* Investigational

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Antiarrhythmic drugs for AF

Risk of therapy

Class I	Class III	Amiodarone
↑ mortality with SHD TDP class IA Atrial flutter 1:1 AV conduction	TDP Women CHF Bradycardia Low K	Non cardiac Thyroid Dermatologic GI Pulmonary Ophtalmologic

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Choix de Traitements Antiarythmiques

	Favoriser	Éviter
Aucune Cardiopathie	Classe Ic, sotalol, amio	Classe Ia, sotalol haute dose chez les femmes
HTA	Classe Ic, sotalol, amio	Classe Ia, sotalol haute dose chez les femmes
MCAS	sotalol, amio	Classe Ia + Ic
Défaillance	amio	Classe Ia + Ic

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Frequently Asked Questions

- Can antiarrhythmic drugs be started in outpatients?
  Only in carefully selected intances because proarrhythmia may occur during initiation of therapy.
- When should attempts to maintain sinus rhythm be abandoned?
  Depends on whether additional agents can be initiated safely and the degree of disability.
- Can anticoagulation be stopped in patients who remain in sinus rhythm while taking antiarrhythmic drug?
  In general, patients should be maintained on anticoagulation because of the high rate of AF recurrence (which is often asymptomatic)

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Common Misconceptions

- Class 1C drugs can be administered without concomitant β-blockers or Ca^{2+} channel blockers.
- Class 1 drugs can be given to patients with structural heart disease

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Supprimer les Extrasystoles Ventriculaires: Étude CAST

N Engl J Med 1991 Mar; 324 (12): 781-8

1498 patients

Encainide — 432 actif, 425 placébo

Flecainide — 323 actif, 318 placébo

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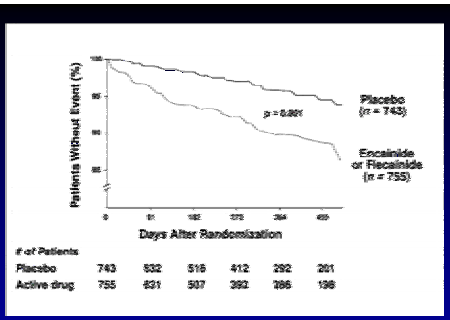

Augmentation significative de la mortalité chez les patients traités avec anti-arythmiques

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CAST

- Stopped early due to excessive mortality in the treatment group
- Primary Endpoint = Arrhythmic death
  - 3% placebo
  - 7.7% for encainide and flecainide
  - If ß-blocker simultaneous then mortality is lower with Class 1C
- Secondary Endpoint = all cause mortality

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Amiodorone Trials Meta-Analysis Investigators

- 8 post-MI trials and 5 CHF trials
- 9 were Double blind and placebo control
- 4 were compared to usual care
- N=6553 followed from 0.4-2.5 yrs
- 78% were post MI trial; 22% CHF trials
- 89% had previous MI
- Mean LVEF = 31%
- Median PVC's = 18/hr

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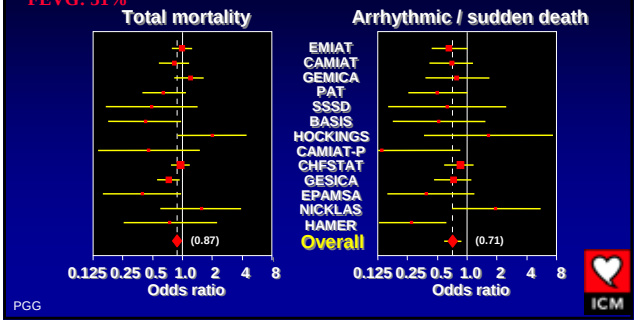
Amiodarone trials meta-analysis (ATMA)

6553 pts
13 études: 8 post-IM, 5 CHF
FEVG: 31%

Lancet 1997



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Amiodorone Trials Meta-Analysis Investigators: Results

- Relative Risk Reduction in all cause mortality with Prophylactic Amiodorone treatment = 13% (p=0.03) OR=0.87
- Most of the effect comes from reduction of arrhythmic or sudden death OR = 0.71 (CI = 0.59-0.85)

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Amiodorone Trials Meta-Analysis Investigators: Conclusions

- Prophylactic use of Amiodorone likely reduces all cause mortality by way of decreasing SCD
- Confirmation from a single large RCT would be desirable but not likely to happen
- Benefit greater in lower LVEF and in patients with symptomatic CHF

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