UNIT FARMASI KLINIKAL (UFK), HUSM.

ATRIAL FIBRILLATION IN CRITICAL CARE – AMIODARONE OR DIGOXIN?

PRECEPTOR:
PN KHAIRUL BARIAH
OBJECTIVES
OBJECTIVES

- To present on management of atrial fibrillation in critical care
- To discuss on the comparison between Digoxin and Amiodarone in management of acute atrial fibrillation.
INTRODUCTION

DEFINITION
CLASSIFICATION
MANAGEMENT
DEFINITION$^{1,2}$

- Supraventricular tachyarrhythmia
- **Uncoordinated** atrial activation

- Atrial
  - Rapid
  - Irregular
  - Chaotic

- **Deterioration** in atrial mechanical function
- Irregular-rapid ventricular response
  - Irregularly-irregular
CLASSIFICATION¹ (1)

First Detected
(One-Diagnosed Episode)

Paroxymal
(< 7 days)

Persistent
(> 7 days)

Permanent
(> 1 year)
CLASSIFICATION¹ (2)

- **Lone AF**
  - No clinical or echocardiographic evidence of cardiopulmonary disease (including HPT)
  - Young patient (<60 years)

- **Secondary AF**
  - AMI, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease.

- **Non-valvular AF**
  - Absence of rheumatic mitral valve disease, prosthetic heart valve or mitral valve repair
<table>
<thead>
<tr>
<th>CLASS</th>
<th>ACTIONS</th>
<th>DRUGS</th>
<th>CAUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Na⁺ channel inhibition: prolong repolarization</td>
<td>Quinidine, procainamide, disopyramide</td>
<td>History of myocardial infarction, congestive heart failure, renal disease</td>
</tr>
<tr>
<td>IB</td>
<td>Na⁺ channel inhibition: shorten repolarization</td>
<td>Lidocaine</td>
<td>Proarrhythmias</td>
</tr>
<tr>
<td>IC</td>
<td>Na⁺ channel inhibition: no effect on repolarization but reduce conductivity</td>
<td>Flecainide, propafenone</td>
<td>Structural heart disease, history of myocardial infarction, congestive heart failure</td>
</tr>
<tr>
<td>II</td>
<td>β-Adrenergic inhibition</td>
<td>Timolol, esmolol, atenolol, bisoprolol</td>
<td>Acute heart failure, bronchospasm</td>
</tr>
<tr>
<td>III</td>
<td>K⁺ channel inhibition: prolong repolarization</td>
<td>Amiodarone, sotalol*</td>
<td>Renal disease, pulmonary disease</td>
</tr>
<tr>
<td>IV</td>
<td>Ca²⁺ channel inhibition</td>
<td>Verapamil, diltiazem</td>
<td>Not in conjunction with β-blockers</td>
</tr>
<tr>
<td>Misc</td>
<td>Na-K ATPase inhibition: parasympathetic response</td>
<td>Digoxin</td>
<td>Renal disease, hypokalemia</td>
</tr>
</tbody>
</table>
Critical Care?

- **Acute Atrial Fibrillation**
  - Onset < 48 h
  - Includes:
    - Paroxysmal AF
    - First symptomatic presentation of Persistent AF
3 Objectives:

- Rate control
- Prevention of Thromboembolism
- Correction of the rhythm disturbance

Rate control ? Rhythm control ?
Conversion to NSR either by electrical (DCC) or pharmacological (AAD) cardioversion.

- Haemodynamically unstable: Electrical
- Haemodynamically stable: Either

Electrical conversion
- Preferred: greater efficacy (85% vs 45%) and low proarrhythmic risk.
- But required generalized anaesthesia
RATE CONTROL

- Slowing AV conduction
- **Slow ventricular response rate → better ventricular filling with blood.**
- If intolerable to S/E of rate-control agent
  - Combining *lower-dose* digoxin + B-blockers/CCBs
- Amiodarone effective for patient who are not cardioverted to NSR.

Good control:
- Rest: 60-80 bpm,
- Moderate: 90-115 bpm
New Onset of AF

Assessment

Haemodynamically unstable

Cardioversion

MANAGEMENT² (2)
Haemodynamically Instability

- Ventricular rates > 150
- Ongoing chest pain
- Evidence of critical perfusion
  - Systolic BP < 90 mm Hg
  - Heart failure
  - Reduced consciousness

To anticoagulate prior conversion if high risk

- Heparin
Acute haemodynamically instability secondary to AF (confirmed by ECG)

Life threatening?

- No
  - Permanent AF
    - Elective electrical cardioversion
    - Rate control (Beta blocker, rate limiting Ca antagonist)
      - Ineffective / contraindicated
      - Amiodarone

- Yes
  - Emergency electrical cardioversion
New Onset of AF

Assessment

Haemodynamically stable

Rate control:
- beta blocker
- diltiazem/verapamil
- digoxin

Consider anticoagulant

Remains in AF

<48hrs
- Anti-arrhythmics ± electric conversion

>48hrs
- TEE-guided cardioversion/3 weeks anticoagulation, then cardioversion
MANAGEMENT$^{1,2}$ (6)

- Focus:
  - Symptom relief
  - Prevention of complications

- Pharmacotherapy
  - Rate Control
    - Class II, Class IV, Digoxin
  - Rhythm Control
    - Class I, Class III, Amiodarone
  - Anticoagulation
Haemodynamically stable

Rate control:
- beta blocker
- diltiazem/verapamil
- digoxin

Consider anticoagulant

Remains in AF

<48hrs
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<tr>
<th>Drug</th>
<th>Recommendation / LOE</th>
<th>LD</th>
<th>Onset</th>
<th>MD</th>
<th>Major S/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol (II)</td>
<td>I / C</td>
<td>500 mcg/kg IV over 1 min</td>
<td>5 mins</td>
<td>60 to 200 mcg/kg/min IV</td>
<td>↓BP, HB, ↓HR, asthma, HF</td>
</tr>
<tr>
<td>Metoprolol (II)</td>
<td>I / C</td>
<td>2.5 to 5 mg IV bolus over 2 min; up to 3 doses</td>
<td>5 mins</td>
<td>-</td>
<td>↓BP, HB, ↓HR, asthma, HF</td>
</tr>
<tr>
<td>Propranolol (II)</td>
<td>I / C</td>
<td>0.15 mg/kg IV</td>
<td>5 mins</td>
<td>-</td>
<td>↓BP, HB, ↓HR, asthma, HF</td>
</tr>
<tr>
<td>Diltiazem (IV)</td>
<td>I / B</td>
<td>0.25 mg/kg IV over 2 min</td>
<td>2-7 mins</td>
<td>5 to 15 mg/h IV</td>
<td>↓BP, HB, HF</td>
</tr>
<tr>
<td>Verapamil (IV)</td>
<td>I / B</td>
<td>0.075 to 0.15 mg/kg IV over 2 min</td>
<td>3-5 mins</td>
<td>-</td>
<td>↓BP, HB, HF</td>
</tr>
</tbody>
</table>
# RATE CONTROL AGENT

<table>
<thead>
<tr>
<th>Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin (Misc)</strong></td>
<td>I / B</td>
<td>0.25 mg IV each 2 h, up to 1.5 mg</td>
<td>60 mins or more</td>
<td>0.125 to 0.375 mg daily IV or orally</td>
<td>Digitalis toxicity, HB, ↓HR</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>Ila / C</td>
<td>150 mg over 10 min</td>
<td>Days</td>
<td>0.5 to 1 mg/min IV</td>
<td>↓BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia</td>
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</tbody>
</table>
**RATE CONTROL AGENT**

### Rate Control (With accessory pathway)

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<tr>
<td>Amiodarone</td>
<td>IIA / C</td>
<td>150 mg over 10 min</td>
<td>Days</td>
<td>0.5 to 1 mg/min IV</td>
<td>↓BP, HB, pulmonary toxicity, skin discoloration, hypothyroidism, hyperthyroidism, corneal deposits, optic neuropathy, warfarin interaction, sinus bradycardia</td>
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</table>

*Intravenous administration of drugs such as digitalis, verapamil, or diltiazem, which lengthen refractoriness and slow conduction across the AV node, does not block conduction over the accessory pathway and may accelerate the ventricular rate. Hence CONTRAINDICATED in AF with accessory pathway. Caution in B-Blockers*
## RHYTHM CONTROL AGENT\(^1,2\)

### COMMON PHARMACOLOGIC Rhythm Conversion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recomm’ / LOE</th>
<th>Conversion Dose</th>
<th>Onset</th>
<th>MD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide (Ic)</td>
<td>I / A</td>
<td>IV 2mg/kg OR 200 mg orally, repeat after 3–4 h</td>
<td></td>
<td>50–150 mg bid</td>
<td>Only for without structural heart disease</td>
</tr>
<tr>
<td>Propafenone (Ic)</td>
<td>I / A</td>
<td>IV 2mg/kg OR 600 mg orally</td>
<td></td>
<td>150–300 mg bid</td>
<td>Only for without structural heart disease</td>
</tr>
<tr>
<td>Amiodarone (III)</td>
<td>IIA / A</td>
<td>6 mg/kg bolus over 30–60 min, then 1,200 mg IV over 24 h</td>
<td>600 mg/d x 1/52, follow by 400 mg/d x 1/52, then 200 mg daily</td>
<td>Moderately effective, slow onset, good HR control; hypotension (bolus dose)</td>
<td></td>
</tr>
<tr>
<td>Sotalol (III)</td>
<td>Not recomm’</td>
<td>5–10 mg slowly IV, may be repeated</td>
<td>120–160 mg bid</td>
<td></td>
<td>Slow Conversion rate; <strong>High proarrhythmia</strong></td>
</tr>
</tbody>
</table>
SR MAINTAINENCE AGENT

Maintenance of Sinus Rhythm

No (or minimal) heart disease

Flecainide
Propafenone
Sotalol

Hypertension

Substantial LVH

No

Flecainide
Propafenone
Sotalol

Yes

Amiodarone
Dofetilide

Catheter ablation

Coronary artery disease

Dofetilide
Sotalol

Amiodarone
Catheter ablation

Heart failure

Amiodarone
Dofetilide

Catheter ablation

Catheter ablation
MANAGEMENT² (8)

Haemodynamically stable

Rate control:
- beta blocker
- diltiazem/verapamil
- digoxin

Consider anticoagulant

Remains in AF

<48hrs
- Anti-arrhythmics ± electric conversion

>48hrs
- TEE-guided cardioversion/
  3 weeks anticoagulation, then
  cardioversion

HEPARIN LMWH

HEPARIN-WARFARIN
Anticoagulation

- In emergency electric conversion (<~/>48h):
  - LD Heparin followed by continuous infusion to keep 1.5-2 x control.
  - Follow by warfarin for at least 3-4 weeks to maintain INR of 2-3.

- In elective conversion:
  - For AF >48hr & haemodynamically stable, anticoagulate for at least 3-4 weeks before & after conversion

- Transoesophageal echocardiography (TEE) performed prior to exclude left atrial appendage clot (↑risk of stroke).
Patients with paroxysmal, persistent or permanent AF

1 Determine stroke/thromboembolic risk

High risk
- Previous ischaemic stroke/TIA or thromboembolic event
- Age ≥75 with hypertension, diabetes or vascular disease
- Clinical evidence of valve disease or heart failure, or impaired LV function on echocardiography

Moderate risk
- Age ≥65 with no high risk factors
- Age <75 with hypertension, diabetes or vascular disease

Low risk
- Age <65 with no moderate or high risk factors

2 Anticoagulation with warfarin

Contraindications to warfarin?

Yes
- Aspirin 75 to 300 mg/day if no contraindications

No
- Warfarin, target INR 2.5 (range 2.0 to 3.0)

Consider anticoagulation or aspirin

Reassess risk stratification whenever individual risk factors are reviewed
DISCUSSION

AMIODARONE OR DIGOXIN?
AMIODARONE\(^3\) (1)

- Benzofuran derivative
- Class III AAD
- IV / Oral
- MOA
  - Potassium channel inhibition
    - Prolongation of the myocardial cell-action potential duration and refractory period
    - All cardiac tissues
  - Noncompetitive \(\alpha\)- and \(\beta\)-adrenergic inhibition
## AMIODARONE (2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>AF Onset</th>
<th>Comparison/Subject</th>
<th>Result / Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peuhkurinen et al</td>
<td>2000</td>
<td>RCT, p=62</td>
<td>&lt;48h</td>
<td>PO amiodarone vs placebo</td>
<td><strong>8h = 50% vs 20%</strong> <strong>24h = 87% vs 35%, p&lt;0.0001</strong> Effective than placebo</td>
</tr>
<tr>
<td>Faniel et al</td>
<td>1983</td>
<td>p=26</td>
<td>-</td>
<td>ICU Patients refractory (either DCC or AAD) were given IV Amiodarone</td>
<td><strong>24h = 80.8% conversion to SR, maintain&gt;48h</strong></td>
</tr>
</tbody>
</table>
| Hilleman et al       | 2002 | Meta-analysis, 18 RCT | <7d      | 1. IV Amiodarone vs other AAD  
2. IV Amiodarone vs placebo | Pooled estimate of cardioversion:  
1) 72.1% vs 71.9%, p=0.84,  
• **No difference, similiar efficacy**  
2) 82.4% vs 59.7%, p=0.03  
• **More effective**  
However, associated with higher risk of pooled estimated adverse effect  
(26.8% vs 16.8% for placebo)  
= Phlebitis, bradycardia, hypotension |
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<tbody>
<tr>
<td>Chevaliar et al</td>
<td>2003</td>
<td>Meta-analysis 13 RCT</td>
<td>-</td>
<td>1. Amiodarone vs Placebo</td>
<td>1) 24h = RR 1.44, p&lt;0.001 • Significant efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Amiodarone vs Class Ic AAD</td>
<td>2) 24h = RR 0.95, p&lt;0.50 • No difference, similar efficacy at 24h – reasonable alternative for class Ic AAD</td>
</tr>
</tbody>
</table>
DIGOXIN$^8$ (1)

- Digitalis glycosides

- Indications:
  - Atrial Fibrillation
    - Ventricular rate control
  - Heart Failure
    - ↑ LV Ejection Fraction
    - Improve symptoms, reduced hospitalisation

- MOA
  - Na-K ATPase inhibitor
  - Vagomimetic effect — ↓ HR & AV conduction
  - ↓ Sympathetic activity — baroreceptor sensitization
## DIGOXIN (2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>AF Onset</th>
<th>Comparison/Subject</th>
<th>Result / Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Falk</strong>&lt;sup&gt;9&lt;/sup&gt; <em>et al</em></td>
<td>1987</td>
<td>RCT</td>
<td>&lt;7d</td>
<td>IVI Digoxin vs Placebo</td>
<td>50% vs 44% *No difference was observed in SR conversion between 2 groups*</td>
</tr>
<tr>
<td><strong>Jordaens</strong>&lt;sup&gt;10&lt;/sup&gt; <em>et al</em></td>
<td>1997</td>
<td>DB-RCT</td>
<td>&lt;7d</td>
<td>IV Digoxin (1.25mg in divided dose) vs Placebo (NS)</td>
<td>30mins = 118 ± 23 vs 139 ± 33, p&lt;0.02 for Ventricular Rate reduction. *However, the persistent stable slowing of heart rate (&lt; 100 beats/min) was only seen in 30% of the non-converted patients randomized to digoxin. *12h = 47.4% vs 40.0% for cardioversion (No Significant difference)</td>
</tr>
<tr>
<td><strong>DAAF Trial Group</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1997</td>
<td>RCT</td>
<td>&lt;7d</td>
<td>IV Digoxin (mean dose 0.88mg) vs Placebo</td>
<td>2h = 105 vs 117, p&lt;0.0001 for Ventricular rate reduction *16h = 51% vs 46%, p=0.37 for SR restoration (No Significant difference)</td>
</tr>
<tr>
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<tr>
<td>Hou et al</td>
<td>1995</td>
<td>R-control study</td>
<td>&lt;10d</td>
<td>IV Amiodarone vs IV Digoxin (as placebo)</td>
<td><strong>Amiodarone:</strong> 157 ± 20 to 122 ± 25 beats/min after 1h, P&lt;0.05; stabilize at 96 ± 25 beats/min after 6 h, P&lt;0.05.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=50</td>
<td></td>
<td></td>
<td><strong>Digoxin:</strong> Fewer dramatic HR alterations, maximum reduction was reached only after 8 h.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>24h = 92% vs 71% were restored to sinus rhythm. The accumulated rates of conversion over 24 h were significantly different between the two groups. P=0.0048.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>“Digoxin, while not as effective as amiodarone in the treatment of recent-onset atrial fibrillation and flutter, appears to be safer.”</strong></td>
</tr>
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<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Joseph et al 3</td>
<td>2000</td>
<td>Prospective RCT, p=120</td>
<td>&lt;24h</td>
<td>Amiodarone / sotalol vs Digoxin (rate control)</td>
<td><strong>Significant reduction</strong> in the time to reversion with both sotalol (13.0±2.5 hours, P&lt;.01) and amiodarone (18.1±2.9 hours, P&lt;.05) treatment compared with digoxin only (26.9±3.4 hours).&lt;br&gt;&lt;br&gt;<strong>48h = 95% vs 78%, p&lt;0.05</strong>&lt;br&gt;&lt;br&gt;The active treatment group was <strong>significantly more likely to have reverted to sinus rhythm</strong> than the rate control group</td>
</tr>
</tbody>
</table>
### AMIODARONE VS DIGOXIN (3)

<table>
<thead>
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</tr>
</thead>
</table>
| Thomas et al | 2004 | R-Digoxin controlled trial. p=140 | -        | Amiodarone (10mg/kg in 30mins) or Sotalol (1.5mg/kg in 10mins) vs Digoxin (500ug in 20mins) (placebo) | Similar rates of pharmacological conversion to sinus rhythm 51% vs 44% vs 50%, p=not significant  
“The overall rates of cardioversion after trial drug infusion and defibrillation were high for all groups (amiodarone, 94%; sotalol, 95%,; digoxin, 98%; P = not significant), but there was a trend toward a higher incidence of serious adverse reactions in the amiodarone group.” |
<table>
<thead>
<tr>
<th>Study</th>
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<th>Comparison/Subject</th>
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</tr>
</thead>
</table>
| Hofmann et al | 2006 | R-Digoxin controlled trial.     | -        | IV bolus amiodarone vs IV bolus digoxin | Baseline HR = 144 ± 19 vs 145 ± 15  
30mins = 104 ± 25 vs 116 ± 23 (p=0.02)  
60mins = 94 ± 22 vs 105 ± 22 (p=0.03)  
Better HR reduction  
SR conversion:  
30mins = 28% vs 6% (p=0.003)  
60mins = 42% vs 18% (p=0.012)  
Amiodarone S/E:  
Asymptomatic hypotension (p=4), Superficial phlebitis (p=1)  
“Amiodarone, given as an intravenous bolus is relatively safe and more effective than digoxin for heart rate control and conversion to sinus rhythm in patients with atrial fibrillation and a rapid ventricular rate.” |
CONCLUSION

- Based on current evidence, amiodarone appears to be more effective and fast in terms of SR restoration in comparison with digoxin.
  - Important in critical care setting
  - Digoxin is not recommended for SR conversion
- Amiodarone also effective in rate control when other agent fails or contraindicated.
- However, amiodarone associated with various adverse effect
  - Close monitoring and precaution is needed
REFERENCES
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