PHARMACY PRACTICE

Therapeutic Alternatives in Atrial Fibrillation

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INTRODUCTION

Atrial Fibrillation (AF) is the most common sustained dysrhythmia. It is more prevalent in the elderly and is a common complication of cardiac surgery. Treatment of AF is often based on previous experience and the most appropriate therapeutic regimen for each patient may not be selected. Therefore, this Therapeutic Alternative Chart for AF was developed to help both medical and pharmacy clinicians choose and utilize the most appropriate therapy for the treatment of AF in a specific patient. Currently the chart is used by practicing pharmacists at St. Michael's Hospital as a tool in providing pharmaceutical care. Additionally, it is used as an educational tool for pharmacists, residents, students, and other health professionals.

METHODS

A thorough review of the current biomedical literature was undertaken using a Medline search of the primary literature back to 1984. All effective agents captured in this literature search were then reviewed specifically for:

a) efficacy in: controlling ventricular response rate (VRR); converting to normal sinus rhythm (NSR); and,
   maintaining NSR after initial conversion;
b) onset of effect;
c) usual dosing regimens;
d) pharmacokinetics;
e) toxicity;
f) drug interactions; and
g) availability/cost.

These agents were also classified into groups by their pharmacologic effects which:

i) only control VRR (i.e., beta-blockers, calcium channel blockers, digoxin);
ii) only convert to NSR (i.e., procainamide, quinidine, disopyramide);
iii) control both VRR and convert to NSR (i.e., sotalol, amiodarone, flecainide, propafenone).

Disopyramide was not included in the chart as the authors felt that its use is quite infrequent secondary to its negative inotropic and anticholinergic effects.

DISCUSSION

While the therapeutic chart only includes esmolol under the beta-blocker row, other beta-blockers would be equally effective when used in equipotent doses to control the VRR. Esmolol was considered the prototype because of its short half-life, and ease of titration. Use of esmolol can demonstrate how a patient will respond to a beta-blocker in terms of causing hypotension or bradycardia. The short half-life of esmolol should ensure a short duration of the adverse effect. Other less expensive beta-blockers such as metoprolol, propranolol, atenolol, and others may be substituted for longer-term control of VRR once response to a beta-blocker has been demonstrated. For the post-operative patient, the intravenous forms of these drugs are used initially because of their more rapid onset; the parenteral forms can be substituted with oral agents once the patient is stabilized and is absorbing enterally. Similar oral conversions for other anti-arrhythmic drugs can also be made.

Although no column in the chart was set aside specifically for the duration of action, the overall duration of action of a drug is a function of the pharmacokinetic half-life (listed on the chart under kinetics), pharmacodynamic half-life, and receptor response (i.e., up or down regulated). The duration of effect may, therefore, differ depending on the patient, the

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Table I: Therapeutic Alternatives in Atrial Fibrillation

Drug	Efficacy	Onset	Dose	Kinetics	Toxicity	Drug Interactions	Comments	Availability/Cost
ß-Blockers* Esmolol (Brevibloc®) Metoprolol Others	VRR = excellent (similar to verapamil)[1] CONV = similar to placebo[2] -may be higher than placebo if hyperadrenergic state[1]	PO = 1-2 hrs IV = 2-5 min (may take longer to titrate)[30]	Complex (multiple bolus infusions) 500 mcg/kg over 1 min then 300 mcg/kg/min x 3 min then 50-300 mcg/kg/min[11]	Ester hydrolysis by RBC esterases. t1/2 = 9 min	bradycardia, symptomatic hypotension (10%)[1, 4, 34] ↓ contractility, ↓ conduction, bronchospasm, ↓ glycogenesis (quick offset with esmolol)	calcium channel blockers, digoxin, disopyramide	-little risk of proarrhythmic effects / torsades des pointes -may aggravate asthma, AV block, diabetes, CHF -benefit in hyperadrenergic post-op patients	IV: 100mg/10ml = $9.48 2.5G/10ml = $134.10
Diltiazem* (Cardizem®)	VRR = 94% bolus[3, 4] = 76% infusion[3, 4] CONV = similar to placebo[5]	IV = 2-5 min[3] (duration 3 hours)[30] PO = 1-2 hrs	0.25 mg/kg over 2 min. If no response in 15 min then 0.35 mg/kg over 2 min then 5-15 mg/hr[11]	Hepatic elimination t1/2=3-5h Active metabolites:[4] desacetyl/N-desmethyldiltiazem	symt hypotension 3%[3, 30] bradycardia, less -ve inotropic effects vs. verapamil[35-38]	ß-blockers, digoxin	- ↓ HR is dose-related - Calcium infusion may decrease hypotension -Use dependent effects[46]	IV: 25mg/5ml = $13.00 50mg/10ml = $24.00 PO: 60mg = $0.33 120mg SR = $0.58
Verapamil* (Isoptin®)	VRR = excellent (similar to diltiazem)[4] CONV = similar to placebo[2]	IV = 2-5 min (30-90 min duration post bolus)[11] PO = 1-2 hrs	2.5-10 mg IV (0.0375-0.15mg/kg) over 2 min then 2.5-10 mg/hr 80-120 mg PO Q6-8h[11]	Hepatic elimination	symt hypotension (10%)[1,30,39], bradycardia, ↓ contractility, ↓ conduction constipation.	ß-blockers diltiazem warfarin digoxin	- Calcium infusion may decrease hypotension[39,47]	IV: 5mg/2ml = $17.80 PO: 80mg = $0.20 120mg = $0.33 240mg SR = $1.33
Digoxin* (Lanoxin®)	VRR = moderate (loss of effect with ↑ adrenergic states)[6,7] CONV = similar to placebo[2,6,8]	IV = 3-4 hrs PO = 4-6 hrs	IV loading = 10-15 mcg/kg (7-11 mcg/kg if renal dysfunction) in divided doses over 24 hours then 0.0625-0.25 mg/day[11]	Renal elimination (May require dose adjustment and/or closer monitoring with ↓ renal function interactions)[32]	bradycardia, nausea, GI effects, arrhythmias, ↑ PR interval, AV block, CNS effects	quinidine, verapamil, diltiazem, amiodarone, cholestyramine, antacids, propafenone[32]	-beneficial effects in LV dysfunction -may require higher plasma level for effect 1-2.6 nmol/L (0.8-2 ng/ml)[32,48]	IV: 0.5mg/2ml = $3.27 PO: 0.125mg = $0.09 0.25mg = $0.09
Procainamide† (Pronestyl®)	VRR = poor CONV = 38-80%[2,9-13] MAINT = ?	IV = 10-30 min PO = 2-4 hrs	10-15 mg/kg IV (max 50 mg/min) then 2-4 mg/min 250-750 mg PO Q3-4h 500-1000 mg SR PO Q6h[11]	Hepatic & renal (50%) elimination. t1/2 = 2.5-5 hrs NAPA is primarily renally eliminated.	proarrhythmia (9%)[40] nausea/vomiting, tremors, hypotension (IV), ANA (SLE-like symptoms) (20-30%), blood dyscrasias (0.5%)[11]	digoxin, amiodarone, cimetidine, trimethoprim	-requires prior VRR control -levels: 4-8 mcg/ml (17-34 µmol/L) -NAPA-toxic/active met (14-29 µmol/L) (may require dose adjustment/ monitoring of levels with ↓ renal function)	IV: 1g/10ml = $10.15 PO: 250mg = $0.18 375mg = $0.23 500mg SR = $0.48
Quinidine† (Quinate®, Cardioquin®)	VRR = poor CONV = 60-80%[2,12-14] MAINT = 50%[15]	IV = 1-2 hrs PO = 4-24 hrs	5-10 mg/kg IV over 30 min (infuse 0.9% NaCl concomitantly to maintain preload).May repeat 400mg iv q2h to max 3g daily. 200-300 mg PO Q6-8h[11]	Hepatic elimination t1/2 = 5-9 hrs F = 0.7 V_D = 3 L/kg	proarrhythmia (15%)[40] Torsades des pointes (1-8%)[41] pain with IV admin./phlebitis nausea/vomiting, diarrhea, cinchonism dizziness, tinnitus, nystagmus (22%) blood dyscrasias[19]	digoxin, amiodarone, warfarin, verapamil	-requires prior VRR control -3% mortality with use[15] -levels: 2-6 mcg/ml (6-18 µmol/L)[48]	IV: 190mg/1ml = $4.98 (sulfate) 800mg/10ml (gluconate) PO: sulfate 200mg = $0.05 gluconate 375mg = $0.26
Propafenone¶ (Rhythmol®)	VRR = moderate to good[16,17] CONV = 51-91%[5,12,13,16,18] MAINT = 30-78%[16,19]	IV = 10-30 min[18] PO = 1-3 hrs	2 mg/kg IV then 2mg/min 150-300 mg PO Q8h[11] (efficacy may be dose dependent)[16]	Hepatic elimination (saturable) t1/2 = 2-10 hrs (fast) (90%) 12-32 hrs (slow) (10%) F = 0.1- 0.2 (non-linear)	proarrhythmia (4-8%)[16,40] ↓ contractility, AV block, hypotension, dizziness(10%), nausea (9%), constipation, tremor, parasthesia, taste changes, (15%)[42]	ß-blockers, calcium channel blockers, digoxin, warfarin, cimetidine	-dose-related ß-blockade (genetic disposition) -active metabolite 5-OH propafenone	IV: 70mg/20ml = ? (emergency release) PO: 300mg = $1.26 150mg = $0.71
Flecainide¶ (Tambocor®)	VRR = moderate[20] CONV = 52-92%[5,9,12-14,19] MAINT = 60%[14,19]	IV = 10-60 min PO = 1-3 hrs	2 mg/kg IV over 10 min. 100-200 mg PO Q12h	Renal (25%) & hepatic elimination. t1/2 = 12-25 hrs	proarrhythmia (4-12%)[40,43] ↓ contractility, blurred vision (30%) nausea, vomiting, dizziness, fatigue (10%)	procainamide, sotalol, amiodarone, digoxin	-use-dependent effects -levels: 0.2-0.8 mcg/ml[48]	IV: ? PO: 100mg = $1.07
Amiodarone¶ (Cordarone®)	VRR = good[20] CONV = 60-80%[10,13,19,21,22] MAINT = 53-87%[14,19,23-27]	IV = 30min -2 hrs[18] PO = 2-10 hrs[31]	5 mg/kg IV bolus over 0.5-1 hr (2 min for emergency) then 5-20 mg/kg/ day over 24 hrs for 5 to 7 days then 200-400 mg PO daily 30 mg/kg PO then 200-400 mg Q1D x 4 weeks then 200-400 mg po daily[11]	Hepatic elimination[24,31,33] V_D = 70L/kg t1/2ß = 9-77 days t1/2_ = 24 hrs F = 0.3-0.65 t_{SS} = months active metabolite (N-desethylamiodarone)	proarrhythmia (<2%)[22] Torsades des pointes (<1%)[44] hypotension (IV), phlebitis (IV) neuropathy (3%), nausea, vomiting, corneal deposits (90%), ↑ LFT's (20%), skin discoloration (3%), pulmonary fibrosis (10%), thyroid dysfunction (30%), photosensitivity (20%), allergic pneumonitis [24,33]	digoxin, warfarin (max effect 4 days), quinidine, procainamide, phenytoin, flecainide, ß-blockers, calcium channel blockers[33]	-no reverse use-dependence effects -fewer hemodynamic effects -has actions of all classes of antiarrhythmics[24,31,48] -levels: 0.5-2.5 mcg/ml -ß-blockade (non-competitive) -polysorbate in IV is a negative inotrope and a vasodilator[49]	IV: 150mg/3ml = $60.00 (approx.) PO: 200mg = $2.01
Sotalol¶ (Sotacor®)	VRR = good CONV = 8-54%[21] MAINT = 50%[28,29]	PO = 2-4 hrs IV = ?	0.5-2 mg/kg IV over 5 min 80-160 mg PO Q12h (efficacy may be dose dependent)	Renal elimination (may require dose adjustment with ↓ renal function) t1/2 = 10-20 hrs. F = 1[29]	Proarrhythmia (4%)[29] torsades des pointes (may be dose related- 2-5%)[1,29,41], AV block, bradycardia, hypotension. see also ß-blockers	ß-blockers procainamide Calcium channel blockers	-reverse use-dependent effects [50] -l-sotalol - class II -d-sotalol - class III -levels: 1.5-4 mcg/ml[48]	IV: ? PO: 80mg = $0.88 160mg = $1.03

* Useful for controlling Ventricular Response Rate (VRR) only † Useful for converting to Normal Sinus Rhythm (NSR)/maintaining NSR only ¶ Useful for controlling VRR, converting to NSR and maintaining NSR

VRR : Ventricular Response Rate Control CONV : Conversion to Normal Sinus Rhythm (variable period) MAINT : Maintenance of Normal Sinus Rhythm once converted (variable period)

dose used, the route of administration, and many other factors. Generally, the stated half-life will give an estimate of how long the drug will provide its given response.

Similarly, the onset of action of these drugs depends on a number of patient and drug specific factors. The listings for onset refer to the onset of activity, **not** necessarily the time to peak effect. In some cases, the peak effect may take days to occur as with amiodarone. Because of amiodarone's long half-life, and large volume of distribution due to a high degree of tissue binding, large loading doses of amiodarone are required for initiation of treatment. The intravenous route of administration of the drug will usually provide a faster onset of action compared to the oral route.

The drug interactions listed in the chart are **not** meant to be all inclusive. Those included were felt to be more commonly encountered and/or clinically significant. Interactions may result in either an increase in effect, with resultant toxicity, or a decrease in effect requiring additional monitoring or intervention. These may include adjustment of doses, withdrawal of a drug or more intense monitoring of clinical effects or toxicities, and serum concentration monitoring. More detail on any of the listed interactions may be found in standard drug interaction references.[45,51-53]

The chart, when used in combination with patient-specific information and clinical judgement, will assist in the rational treatment of patients with AF. No one drug or drug combination listed in the chart is the drug of choice for every patient. The chart is useful because **all** the potential options are listed, and best regimen for a specific patient may be selected. Some of the specific patient information required before a rational choice for treatment of AF can be made includes assessment of:

- patient demographics (i.e., age, level of physical activity, etc.);
- cardiac conditions including:
  - left ventricular function;
  - left atrial size;
  - hemodynamic effect of the arrhythmia;
  - duration of dysrhythmia;
  - heart rate; and
  - cardiac conduction abnormalities.
- renal/hepatic function;
- pulmonary function (reversible airway disease);
- serum electrolytes and fluid status;
- thyroid function;
- past or present antiarrhythmic usage and present drug therapy;
- sympathetic state of patient (e.g., pain control, recent stress, etc.);
- other disease states (e.g., diabetes, etc.);
- patient preferences (i.e., adverse effects, drug plan coverage, etc.).

The approach to the patient with AF would first be to treat any underlying risk factors such as hypomagnesemia, hypokalemia, or hyperthyroidism. Consideration should be given towards withdrawal or dosage reduction of any arrhythmogenic medications the patient is receiving. These could include theophylline, catecholamines, thyroxine, etc. The patient should then be assessed to determine the hemodynamic effects of the arrhythmia. If the AF is causing hemodynamic compromise, electrical cardioversion may precede pharmacologic conversion. If the AF is new in onset, the goal of therapy would be to return the patient to normal sinus rhythm without any adverse drug effects. Initial control of AF may be achieved by controlling the rate with either beta-blockers, calcium channel blockers, or digoxin. Beta-blockers, which are normally useful only for rate control may be helpful in conversion of a patient with a hyperadrenergic state (e.g., post-operative patients). These and other rate controlling drugs can decrease the hemodynamic and symptomatic effects of the arrhythmia in preparation for electrical conversion, pharmacologic conversion with procainamide or quinidine, or chronic rate control along with adequate anticoagulation.[34] Alternately, combined rate control and conversion to NSR may be achieved with amiodarone, flecainide, propafenone, or sotalol.

When using the chart, consider various factors about the patient and disease state of AF. Up to 40% or more of patients with recent onset AF (<48 hours) convert spontaneously to NSR.[13] Unfortunately, approximately 75% of patients experience recurrence of the AF[15,27,28] thus, some patients may require maintenance antiarrhythmic therapy to improve the chance of maintaining NSR. Patients with heart failure, enlarged left atrial size (> 45 mm), and longer duration of AF (> 2 months) have a smaller chance of remaining in NSR once converted.[14] Patients whose AF was related to a definite risk factor which has been corrected e.g., electrolyte disorder, drugs, or hyperadrenergic state have a better chance of staying in NSR. In determining whether to employ maintenance antiarrhythmic therapy, the risks of drug treatment including the possibility for side effects, proarrhythmia and even increased mortality should be weighed against the risk of reverting back into AF, which although bothersome is not usually fatal.

In the acute setting of AF, a number of treatment choices are available including: controlling the VRR, controlling the VRR and converting pharmacologically or electrically or converting electrically. If the AF converts to NSR, the treatment options include: the use of VRR controlling agents to prevent rapid ventricular response if the patient reverts back to AF; using antiarrhythmic agents to increase the chance of remaining in NSR; or no therapy at all.

If the AF is felt to be resistant to conversion, chronic control of VRR may be employed with anticoagu-

lation to help prevent thrombotic complications.

Our experience at St. Michael's Hospital documents efficacy in AF control with many of the drugs listed on the chart. A commonly used drug for converting AF to NSR is procainamide, although a drug regimen of choice should be chosen with a specific patient in mind. Amiodarone, and more recently sotalol are becoming more frequently utilized. The enthusiasm for the long-term use of amiodarone is curtailed by its many, and potentially serious adverse effects, and its cost. The Class Ic antiarrhythmic agents (flecainide, propafenone) may not be used as frequently because of their concern over proarrhythmia,[54] especially for patients at higher risk who may have structural heart disease, decreased left ventricular function, and prior ventricular arrhythmias.[54,55] It has been suggested that patients with atrial arrhythmias may not be at high risk for proarrhythmia, however, others have cautioned that AF itself may be a risk factor for proarrhythmia, possibly because patients with AF frequently have underlying organic heart disease.[22,43,56] Flecainide should be used cautiously in high risk patients, starting with low initial doses titrated slowly every five half-lives, while monitoring serum drug concentrations and the electrocardiogram.[57] Propafenone may have significant proarrhythmic properties as it also is in Class Ic. It may be of lower risk than other drugs in this class because of its beta-blocking properties which may protect against proarrhythmia.[16,58] The specific benefits and adverse effects of all the potential drugs listed must be weighed using specific patient information.[41]

We have found the chart to be a useful tool in helping provide pharmaceutical care to our patients experiencing atrial fibrillation. In addition, it also has been well-received by the medical housestaff. When used in conjunction with patient-specific information, the chart is helpful in assessing the many pharmacologic alternatives for the treatment of atrial fibrillation. We believe that the development of Therapeutic Alternative Charts for other disease states would be useful to help improve patient specific therapeutic decision making and to increase the visibility and responsibility of pharmacists in contributing to patient care.

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