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Could You Use These New Cardiac Drugs in Your Practice?

New cardiovascular drugs, including intravenous ACE inhibitors, ?-blockers for congestive heart failure, and medications for ventricular tachycardia and atrial fibrillation, may be useful in your practice. The literature on these new drugs will be reviewed, and a comparison with currently available medications will be made.

- Identify what new drugs are available for the treatment of cardiac patients.
- Discuss the advantages and disadvantages of these new cardiovascular drugs.
- Discuss the literature that describes the use of these drugs.

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FACULTY

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Could These New Cardiac Drugs Change Your Practice

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Introduction:

The past several years have seen a veritable explosion of new therapies in the area of cardiovascular medicine. Not only are many new drugs being introduced on the market but currently existing drugs are being used in new ways, with new indications and increasingly with direct applications to Emergency Medicine. With the advent of "Heart ERs", observations units, and the trends toward earlier, aggressive management of cardiac disease, the world of inpatient cardiology is being transplanted to the ED. As a consequence, ED physicians are increasing being confronted with 'cutting edged' therapies outside our traditional practice. The following discussion will focus on five common cardiovascular syndromes using case based scenarios. New therapies will be reviewed in terms of their indications, side effects, and advantages over current standard therapy.

New Onset Atrial Fibrillation

Atrial fibrillation affects 1 -2 % of the adult patient population and is a common presenting problem in the ED. Thinking teleologically and addressing the root cause of the arrhythmia may be the most important determinant of successful management. When A-fib manifests with a rapid ventricular response, there are essentially two principal treatment objectives: rate control and restoration of sinus rhythm. Our potential for success in either of these objectives is determined by a variety of factors: choice of antiarrhythmic, dose and mode of delivery, and perhaps most importantly, the characteristics of the patients themselves. For this reason, the success rates for conversion and rate control for the different therapies vary wildly from study to study depending largely on the patient selection criteria.

Rate Control:

- The spectrum of symptomatology in A-fib is broad, ranging from an asymptomatic condition in older, less active individuals with slower ventricular responses to severe, life threatening symptoms: angina, congestive failure, or syncope. The indication and method of rate control must take the overall patient condition into account. Tailor the degree of rate control to fit the clinical situation; rapid rates may be adaptive and appropriate in the setting of sepsis, fever to 103, etc. There are three types of antiarrhythmic drug used to slow ventricular rate; each acting by blocking antegrade conduction through the AV node: Digoxin, Beta-blockers and Calcium channel blockers.

Digoxin:

This traditional therapy is less popular in light of new evidence regarding its lack of effectiveness in some A-fib patients, its potentially proarrhythmic effects, and the arrival of newer more effective agents.

<u>Mechanism/Pharmacology</u>: The predominant effects of digoxin are mediated

through the autonomic nervous system. In the resting digitalized patient, vagal tone at the AV node is increased resulting in parasympathetic mediated slowing of ventricular response. This effect is largely overridden in situations of increased sympathetic tone; which accounts for the failure of digoxin to control paroxysmal A-fib.

Advantages:

- long, established history of use.
- inexpensive
- once-a-day dosing with measurable serum levels
- improves inotropy in patients with congestive heart failure. Improved hemodynamics may result in cardioversion if A-fib is of recent onset.
- controls "resting" heart rate in "most" patients with chronic A-fib, particularly in those with sedentary life styles

Disadvantages:

- slow delivery and onset of action
- rate control is largely vagal mediated and easily reversed by increased sympathetic tone. Compared to placebo, patients with paroxysmal A-fib experience no added benefit when taking digoxin. Similarly, patients with high resting sympathetic tone maybe refractory to digitalization.
- Patient with paroxysmal A-fib may experience more frequent and more protracted episodes of A-fib when taking digoxin compared to placebo. This is more than a theoretical disadvantage since more A-fib means more complications of A-fib and may also promote remodeling of the atria rendering A-fib more intractable (A-fib begets A-fib phenomenon).
- digoxin is ineffective in maintaining normal sinus rhythm once cardioversion has occurred. Furthermore, digoxin may actually lessen the effectiveness of Quinidine when used in combination.

Diltiazem

Calcium channel blockers have a direct slowing effect on AV nodal conduction. They are effective in slowing ventricular response both at rest and with exercise. Diltiazem has largely supplanted Verapamil because it has less negative inotropy and can be given as a continuous infusion for up to 24 hours.

Mechanism/Pharmacology:

- Blockage of slow calcium channels.
- IV bolus of 20 mg over 2 minutes, repeated after 15 minutes if response inadequate. Continuous IV infusion of 10-15 mg/hr can be started immediately after the initial bolus.

Advantages:

- IV dosing with rapid (~ 5-10 minutes mean response time)
- highly effective in controlling rapid ventricular response compared to

placebo.

- effective even in the setting of congestive heart failure. In patients with severe left ventricular dysfunction (NY Heart Assoc class III, IV) diltiazem was well tolerated (no observed clinical deterioration) and produced a net decrease in heart rate, and pulmonary vascular resistance and a net increase in average stroke volume and cardiac output.

Disadvantages:

- low incidence of conversion to sinus in comparison other antiarrhythmic agents. Conversion rates higher than with placebo - however, may represent improved hemodynamics rather than a direct antiarrhythmic effect
- must be avoided in the setting of WPW and rapid A-fib due the risk of deterioration to lethal ventricular tachyarrhythmia
- increased observed mortality associated with the use of calcium channel blockers in the peri-infarction period (if continued after rate control achieved). Two studies have shown improved short-term survival in non-Q wave MIs using diltiazem (only).

Beta-blockers

The mechanism and profile of beta-blockers for rate control of A-fib is similar to that of verapamil. The negative inotropic effects severely limit their use in patients with LV dysfunction. Esmolol (rapid short acting beta-blocker) has been used effectively for rate control yet hypotension is a common complication and dosing protocols are cumbersome and complex. One study suggested that the combination of digoxin and esmolol may mitigate these negative side effects, provide the patients had no absolute contraindications to beta-blocker use (severe COPD, class IV CHF)

Conversion of A-fib

The indications for conversion of A-fib overlap somewhat with those of rate control. The severely symptomatic patient may be best served by expeditious conversion: either electrically or pharmacologically, provided there are no contraindications (risk of thromboembolism). Traditional teaching allows immediate cardioversion without anticoagulation if the A-fib is of < 48 hours duration. Longer episodes of A-fib require 3-4 weeks of anticoagulation or TEE evaluation and acute heparinization. The 'Gold Standard' is DC cardioversion which restores normal sinus rhythm in about 85% of cases. One must remember, however, that the single most important determinant of success in the conversion of A-fib is the duration of the arrhythmia. Spontaneous conversion occurs in ~ 50% of cases if the A-fib is of recent onset. The addition of procainamide will convert 91% of A-fib of less than 2 days duration. This rate fails off precipitously to 33% for episodes lasting more than 2 days. Therefore, as stated above, relative comparisons of the various new therapies must take into account the important potential bias of patient selection.

Digoxin, calcium channel blockers, beta-blockers, and Sotalol

- each of these agents has been studied in relationship to its ability to

restore sinus rhythm. Results vary widely between studies. In head-to-head studies with matched populations, none performs better than Amiodarone or Ibutilide. The conversion rates seen probably reflect improvement in hemodynamics due to rate control among other effects.

Amiodarone

Amiodarone is a class III antiarrhythmic which has been recently approved by the FDA for IV treatment of refractory ventricular tachycardia. There is, however, a large body of literature supporting its use in the conversion of A-fib, particularly as an oral agent. The overall rate of conversion of a-fib is highly variable with amiodarone and probably lower than the Type I agents. However, because of it safety in patients with poor left ventricular function and the relatively low incidence of proarrhythmia, it may still have a role to play.

Mechanism/Pharmacology:

- class III antiarrhythmic, mild beta-blocking activity, peripheral vasodilation
- oral and IV preparations: Dosing IV 3-5 mg/kg infusion over 10 minutes - followed by an infusion of 5 mg/kg every 8 hours
- mild negative inotropic effects together with peripheral vasodilation causes hypotension in ~ 10% of patients(no change in CO) - effects usually transient and well tolerated. Risk of hypotension related to rate of infusion

Advantages:

- effectiveness is highly variable with small published studies reporting conversion rates ranging from 4 - 100%. In one study, mean time to conversion was 10 hours. Two studies found no improvement over placebo in converting atrial arrhythmias.
- mitigated effects on blood pressure compared to other type Ia and Ic drugs.
- Beta blocking effects slow ventricular response.
- can be used effective in conjunction with other agents
- blocks equally AV conduction and accessory pathways - useful in WPW

Disadvantages:

- variable effectiveness
- significant time to conversion despite IV dosing
- sides effects when given long term therapy only: pneumonitis, liver enzyme rise, bluish skin discoloration, hypo or hyperthyroidism, increases Coumadin effects

Ibutilide

Ibutilide is novel intravenous antiarrhythmic with class III antiarrhythmic properties. It is the first IV antiarrhythmic since procainamide to specifically target atrial tachyarrhythmias and is being marketed as the pharmacologic equivalent of DC cardioversion.

Mechanism/Pharmacology:

- Class III antiarrhythmic - prolongs action potential and increases refractory period

- Dosing: 1 mg IV infusion over 10 minutes, followed 10 minutes later by a second 1 mg infusion over 10 minutes. Usually effective within one hour
- QT prolongation correlates with plasma levels and is an expected ECG finding. The possibility of Torsades de Pointes should be anticipated: immediate access to a cardiac defibrillator, IV magnesium and transcutaneous pacing.
- There is no affect on heart rate, blood pressure, cardiac output, pulmonary arterial pressure, or wedge pressure. (Procainamide is known to cause significant hypotension)

Advantages:

- Conversion rates of A-fib on the order of 50 - 88% using the 1 mg and 1 mg dosing scheme. Comparison trials of sotalol and procainamide with ibutilide showed a 2-3 fold greater chance of conversion with the latter. There are no direct comparison studies of amiodarone and ibutilide, however, Dofetilide (related drug) was found to be far superior to amiodarone for the conversion of A-fib.
- No affect on blood pressure, heart rate, or cardiac output makes this an excellent choice for use in patients with compromised left ventricular function.

Disadvantages:

- Proarrhythmic effects - overall incidence of torsades de pointes is 4.3%- 8.3 % with 1.7 % of patients requiring some form of intervention to convert the polymorphic tachycardia. In each case, the torsade de pointes occurred within 1 hour of the infusion and all were successfully treated. 4.9 % of patients experienced non-sustained monomorphic ventricular tachycardia. This second category of arrythmia is not significantly more common than with other comparison drugs or placebo. Authors recommend anticipating having to treat torsades de pointes and avoiding the use of ibutilide in patients prone to this rhythm (previous history, coexistent I-A drugs or prolonged Q-T syndrome.
- Ibutilide will not reliable maintain normal sinus rhythm after conversion. Once sinus rhythm is restored, a second agent (usually quinidine, pronestyl or amiodarone) should be added

Bottom line:

Rate Control:

-Digoxin: benign but relative ineffectual role in the ED management of A-fib - slow rate control, little better than placebo, may potentiate long term a-fib, best used for chronic rate control in elderly patients with CHF

- Diltiazem: best single choice for rate control, even if poor LV function.

Conversion:

- DC cardioversion: best choice for symptomatic patient
- Ibutilide: useful in patients for whom DC cardioversion is not

desirable - rapid, early onset on action, hemodynamically stable - anticipate Torsades de pointes.

- Amiodarone: best second choice drug after Ibutilide, particularly in the setting of LV dysfunction (relatively CV stable)

Sotalol

Sotalol is a class III antiarrhythmic (like aminodarone -prolongs ventricular refractory period) with simultaneous beta-blocking effects that are approximately 30% that of propranolol. Sotalol is currently FDA approved for oral treatment of life-threatening ventricular arrhythmias. The IV form used outside the US has been shown to be effective in rate control of SVT and A-fib, although conversion rates are lower than amiodarone in head-to-head comparison studies. For SVT and A-fib with WPW, sotalol has the theoretical advantage of blocking both the antegrade and accessory pathways making it a potential alternative to procainamide in these patients.

Propafenone

Newer class Ic antiarrythmic with both atrial and ventricular activity. Oral loading found to be similar in efficacy to a number of mainstay agents in head-to-head trials. Most common indication as a maintenance drug for a-fib post conversion in lieu of quinidine or amiodarone.

Ventricular tachycardia/fibrillation

Traditional therapy for ventricular tachycardia, either sustained or intermittent follows standard ACLS guidelines: Lidocaine, followed by either procainamide or bretylium. Lidocaine has a low efficacy rate, on the order of 18% in recent studies. Procainamide has the disadvantage of long loading times (~ 50 minutes) and relatively frequent complications of hypotension and polymorphic V-tach. Bretylium is conveniently dosed but causes significant hypotension, occasionally lasting for days.

IV Amiodarone was recently approved for treatment of refractory V-tach (ie when other traditional therapies fail). Sotalol is currently only approved for PO use but be a useful adjunct once it appears in IV form.

Amiodarone

Mechanism/Pharmacology:

- Class III - prolongs refractory period, Beta and calcium channel blocking effects - net effect on myocardium is mild negative inotropy and peripheral vasodilation.
- dosing: variable regimens described: 150 mg infusion over 10 minutes, followed by 1 mg/min for next 6 hours, 0.5 mg/min thereafter.

Advantages:

- highly effective in refractory V-tach - 60-80% conversion suppression rates- similar effectiveness to bretylium with 50% less hypotension.
- acts to suppress supraventricular arrhythmias as well(see above)

Disadvantages:

- liver and thyroid abnormalities (seeabove)

Bottom line

- lidocaine is still first-line therapy along with DC cardioversion.
- amiodarone appears to have significant advantages over bretylium as a second or third line drug - particularly in patients with compromised LV function

Congestive heart failure

Congestive heart failure is a dynamic and multifactorial syndrome. Management algorithms must take into account the etiology of the failure as well as the patient's prevailing cardiovascular status. Newer therapies include IV Enalapril for 'acute' CHF and/or hypertensive urgencies, and the use of beta-blockers (carvedilol) in compensated, severe 'chronic' heart failure.

Enalapril (IV)

Mechanism/Pharmacology:

- ACE inhibitor, vasodilator,
- Dosing: 1.25 mg IV q 6 hours,

Advantages:

- rapid onset, potent vasodilator with no negative inotropic effects
- allows acute control with IV agent and easy tradition to oral therapy.

Disadvantages:

- ACE side effects: cough, angioedema, hypoglycemia (may be alleviated by using losartin "Cozar")

Fenoldopam: arteriolar vasodilation through stimulation of Dopamine $_1$ receptors. Alternative to nitroprusside, IV infusion agent which produced a rapid reduction in MAP while increasing renal blood flow, urine output.

Mechanism/Pharmacology

- peripheral dopamine -1 (DA_1) agonist.
- 0.1 - 1.6 ug/kg/min, no bolus needed
- titratable, infusion , plasma elimination T1/2 = 5 minutes

Advantages:

- easy on, easy off,
- maintains or improves renal blood flow

Disadvantages:

- risk of excessive hypotension
- may cause increased intra-ocular pressure (avoid in glaucoma)

Carvedilol

Beta blockers are increasing being use in the management of severe chronic heart failure with dramatic results. Previously, beta blockers were felt to be contraindicated in heart failure due their negative inotropic effects. Several lines of evidence suggest that a major contributor to the pathology and progression of CHF is excessive activation of the sympathetic nervous system. While a heightened

sympathetic tone is adaptive for the heart, there are several other compensatory effects which are more detrimental: stimulation of the renin-angiotensin system, enhance sodium and water retention, vasoconstriction and subsequent increased pre and afterload. A vicious cycle ensues leading to even greater LV dysfunction. Beta blockade appears to benefit even severe (NY class IV) CHF by antagonizing over the long term these less adaptive neurohormonal systems. This is in addition to the considerable beneficial effects of beta-blockers and their impact on mortality (see table). The newer Carvedilol represents one of the best examples of this phenomenon.

Mechanism/Pharmacology:

-Beta blocker with some alpha blocking effects, also possesses mild antioxidant effects.

- Oral dosing only; 6.25 mg BID advancing to 50 mg BID as tolerated

Advantages:

- significant improvement in all phases: mortality, progression of disease, need for hospitalization.
  - 65% lower risk of death extending out 15 months
  - 26 % reduction in hospitalization
- provides all the ancillary benefits of Beta blockade

Disadvantages:

- not appropriate for acute exacerbations, 33% vs 20 of placebo group experienced dizziness (most other categories were similar)
- requires slow and carefully managed dosing
- 5% experienced a transient worsening of their status, incidence partially offset by very gradual loading of the drug.

Bottom line:

- not yet appropriate for the ED, or in unstable decompensated CHF
- excellent choice for stable outpatient CHF, particularly of CAD origin due to crossover beneficial effects.

Unstable angina

The use of heparin therapy has been shown to be of benefit in unstable angina as well as an adjunct to TPA thrombolysis in acute MI. Recently, low molecular weight heparin (**Enoxaparin**) has been suggested as an alternative to IV heparin in light of beneficial results seen in DVT and Pulmonary embolus management. In comparison studies, LMWH has proven to be more effective, safer, and convenient than standard heparin infusion.

Dosing: Enoxaparin 1 mg/kg BID SQ

Platelet aggregation at the site of a ruptured plaque is a dominant feature in the pathophysiology of unstable angina. Accordingly, antiplatelet therapy in the form of aspirin has become commonplace in both MI and unstable angina. **Reopro** (Abciximab) is a new agent (others include eptifibatide '**Integrilin**' and tirofiban '**Aggrastat**') which functions as a potent inhibitor of platelet aggregation by blocking the GPIIb/IIIa receptors on the platlet. Its principal role is as an adjunct to PTCA for patients with refractory unstable angina. In the CAPTURE study, Repro was found to significantly reduce thrombotic/MI complications prior to and following PTCA. The 30 endpoint of death, MI or the need for repeat intervention occurred 29% less often in the Reopro group compared to placebo. Bleeding complications were rare in either group

but slightly more common with Reopro. The EPIC and EPISTENT studies found an extended favorable outcome even at 6 months, but primarily in patients receiving both PTCA and stent placement. The results for eptifibatide and tirofiban were less conclusive (PURSUIT, RESTORE, PRISM).

Mechanism/Pharmacology:

- inhibitor of platelet aggregation
- IV bolus of 0.25 mg/kg followed by an infusion of 10 ug/min
- Heparin should be added, 100 units/kg or 10,000 units whichever is less. Excessive heparinization may result in bleeding complications. Recent evidence suggests that low dose heparin may be safer and equally effective (NEJM)

Thrombolytics:

Reteplase (r-PA) is the newest thrombolytic to enter the fray and more are promised soon. New generation t-PAs primarily add convenience in dosing by extending the serum half-life of the agent. Traditional t-PA has a half-life of 3 minutes and must be given as an infusion. Reteplase is deletion mutant plasminogen activator must be "unfolded" in the body to be activated. T ½ of reteplase is 18 minutes allowing the drug to be given as two boluses 30 minutes apart.

The RAPID I & II trials comparing t-PA with r-PA found small but significant improvements is 60 and 90 minutes patency rates with reteplase vs traditional and accelerated t-PA. Reteplase also led to fewer acute coronary interventions with a safety profile similar to standard t-PA.

The INJECT trial compared r-PA to streptokinase (STK) in 6010 patients. The two end points of 35 day and 6 month mortality or grave disability found no significant differences between the two agents. The r-PA group experienced more hemorrhagic strokes (0.77% vs 0.37%) but had fewer in-hospital events.

Overall mortality data awaits the results of the GUSTO III trial. Previous data would suggest that earlier and improved patency rates (TIMI class III flow) will translate to improved survival.

Mechanism/Pharmacology:

- modified tissue plasminogen activator, T ½ = 18 minutes
- Dosing: 10 units IV bolus, repeat 10 units in 30 minutes
- requires IV heparin: 5000 units bolus followed by infusion to maintain PTT at 1.5 -2.0 of normal, and aspirin.
- cost : same as t-PA ($2200 per patient)

Advantages:

- convenience in dosing
- possible improvement over t-PA and STK in terms of patency rates. - overall mortality statistics pending.
- similar safety profile to t-PA

Disadvantages:

- cost
- higher rate of bleeding complications compared with STK

TNK and **NPA** : Newests thrombolytic agent with single IV bolus dosing regimen. Recently reported large multicenter trial (~32,000 patients) ASSENT II and INTIME II found 30 day mortality and complication

rates identical to traditional t-PA.

Bibliography

1) Falk R, Leavitt J. Digoxin for atrial fibrillation: A drug whose time has gone? Annals of Internal Medicine. 1991. 114, pg 573.
2) Heywood J, et al. Effects of intravenous diltiazem on rapid atrial fibrillation accompanied by congestive heart failure. American Journal of Cardiology. 1991, 67, pg 1150
3) falk R, et al. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm: A randomized double blinded trial. Annals of Internal Medicine. 1987, 106, pg 503
4) Kowey P, et al. Intravenous amiodarone. J American College of Card. 1997, 29, pg 1190
5) Pritchett E. Management of atrial fibrillation. New Eng J. Med. 1992, 326, pg 1264
6) Anderson J. Acute treatment of atrial fibrillation and flutter. Amer J Card. 1996, 78, pg 17
7)Ellenbogen K, et al. Efficacy of ibutilide for termination of atrial fibrillation and flutter. Amer J Card. 1996, 78, pg 42
8) Stambler B, et al. Efficacy and safety of repeated intravenous doses of ibutilide for the rapid conversion of atrial flutter or fibrillation. Circulation. 1996, 94, pg 1613
9) Kowey P et al. Randomized double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. Circulation. 1995, 92, pg 3255
10) Sacker-Bernstein J, Mancini D. Rationale for treatment of patients with chronic heart failure with adrenergic blockade. JAMA. 1995, 274, pg 1462
11) Packer M, et al. The effect of carvedilol on morbidity in patients with chronic heart failure. New Eng J Med. 1996, 334, pg 1349
12) Hirschl M, et al. Clinical evaluation of different doses of intravenous enalapril in patients with hypertensive crises. Arch Int Med. 1995, 155, pg 2217.
13) Langes K, et al. Efficacy and safety of intravenous captopril in congestive heart failure. Curr Ther Res. 19993, 53, pg 167.
14) The CAPTURE investigators. Randomized placebo controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet. 1997, 349, pg 1429.
15. Bode C, et al. Patency trials with reteplase (r-PA): What do they tell us ? Amer J Card. 1996, 78, pg 16.