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4:30

COST-EFFECTIVENESS ANALYSIS OF ANTIARRHYTHMIC AGENTS

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The Cardiac Arrhythmia Suppression Trial (CAST) results have highlighted the potential adverse effects of all antiarrhythmic agents. Quinidine (QUIN) and procainamide (PROC) have the potential for major organ toxicity. In contrast, mexiletine (MEX) has been reported to have little risk of organ toxicity, a low incidence of serious proarrhythmia and CHF, but a relatively high incidence of nuisance side effects (SE). Thus, we assessed the relative cost-effectiveness of the three agents. We compared MEX, QUIN, and PROC for use in ventricular arrhythmias based on a review of 1000 published reports, including foreign language articles with English abstracts. Studies included in the analysis considered at least one of the agents, in adults, with adequate efficacy and/or safety data. Data were analyzed using a decision analysis/cost-effectiveness model. Probabilities were averaged using techniques of meta analysis. Costs were taken from a university medical center cost allocation model. Thirty-seven separate SE were included in the analysis. In terms of overall cost, 12 months of MEX would engender $1407, QUIN $2740 and PROC $2844 of expenses. MEX dominates the older agents in terms of cost-effectiveness, a result that holds over a wide range of efficacy and safety data. These results are preserved through probabilistic sensitivity analysis, in which MEX is the least costly drug over 12 months of treatment. Our results suggest that MEX is a cost-effective alternative therapy for ventricular arrhythmias.

5:00

THE ELECTROCARDIOGRAPHIC EFFECTS OF ENCAINIDE, FLECAINIDE, AND MORICIZINE IN A SUBGROUP OF THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL

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We evaluated the effects of encainide, flecainide, and moricizine on computerized ECG intervals during the open-label titration phase of Cardiac Arrhythmia Suppression Trial (CAST) at the Minnesota site. We enrolled 106 patients (pts), who received 124 drug trials (43 encainide trials, 46 flecainide trials, 35 moricizine trials). Computerized ECG intervals were measured on each dose (Hewlett Packard Model 5600C). The variability (standard deviation) of this system in our laboratory is 2.4 ms for PR, 1.6 ms for QRS, and 6.8 ms for QTc. On maximum dose, we observed the following ECG changes from baseline.

	mean dose (mg/day)	ΔPR (ms)	ΔQRS (ms)	ΔQTc (ms)	ΔJTc (ms)
Encainide	120 ± 21	18 ± 21 *	19 ± 17 * a	11 ± 38 *	-8 ± 37
Flecainide	228 ± 46	25 ± 20 *	13 ± 12 *	5 ± 28	-7 ± 29
Moricizine	694 ± 97	18 ± 21 *	11 ± 12 *	-6 ± 23 b	-17 ± 25 *

*) $p < 0.05$ versus baseline. a) $p < 0.05$ versus flecainide and moricizine. b) $p = 0.055$ versus encainide.

CAST involved several subcategories of treatment based on left ventricular ejection fraction and response to therapy. We compared the 3 drugs in the following subcategories: 1) encainide vs moricizine as the initial randomization drug (n = 11), 2) encainide vs flecainide as the initial randomization drug (n = 78), 3) encainide vs moricizine in patients treated with both drugs (n = 10), 4) flecainide vs moricizine in patients treated with both drugs (n = 10), and 5) the 3 drugs compared in those patients who had suppression of arrhythmia on the drug (n = 102). The above changes in ECG intervals were confirmed when we compared pts in each of these subcategories.

Although therapeutic doses of encainide, flecainide, and moricizine all had class IC ECG effects in our study (increased PR and QRS but not JTc), there were differences among the drugs that were not accounted for by the IA-IB-IC system and indicate the potential weakness of this system. Encainide caused more prolongation of the QRS whereas moricizine shortened the JT interval more than the other drugs. These findings indicate the unique nature of antiarrhythmic drugs, including drugs within the same subclass.

4:45

A DOSE RESPONSE STUDY OF INTRAVENOUS DILTIAZEM FOR THE TREATMENT OF ATRIAL FIBRILLATION AND FLUTTER

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We performed a randomized double-blind placebo-controlled trial to evaluate the safety and efficacy of 4 doses of intravenous (IV) diltiazem in the treatment of pts with atrial fibrillation (A FIB) or atrial flutter (A FLUT). Fifty pts (age 63 ± 14 yr) with spontaneous A FIB or A FLUT at a heart rate (HR) ≥ 120 bpm received either a 2-minute injection of placebo (n=15) or diltiazem (0.05 mg/kg, n=9; 0.15 mg/kg, n=8; 0.25 mg/kg, n=10; 0.45 mg/kg, n=8) followed by 15 minutes of observation. Table provides mean % change in heart rate, response rate, and mean % change in systolic and diastolic blood pressure (SBP/DBP) for each dose. Response was defined as either ≥ 20% decrease in HR, HR < 100 bpm, or sinus rhythm.

	Diltiazem (mg/kg)				
	Placebo	0.05	0.15	0.25	0.45
HR change	-4%	-10%	-20%	-25%	-26%
Response rate	13%	44%	62%	80%	75%
SBP/DBP	-3/-3%	0/-3%	-4/-3%	-9/-10%	-13/-7%

The linear relationship between HR reduction and dose was significant ($p < 0.001$); however, only the 0.15, 0.25, and 0.45 mg/kg doses of diltiazem were more effective ($p < 0.001$) than placebo. The most frequent adverse event was a transient hypotension, which occurred with similar frequency in pts receiving 0.15, 0.25, or 0.45 mg/kg, and was symptomatic in only 3 pts. In conclusion, IV diltiazem in doses of 0.15, 0.25, and 0.45 mg/kg safely and effectively reduces HR in pts with A FIB or A FLUT.

5:15

SAFETY AND EFFICACY OF INTRAVENOUS SOTALOL IN TERMINATING SUPRAVENTRICULAR TACHYARRHYTHMIAS

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Sotalol (S) is a new antiarrhythmic agent with both beta-adrenoceptor blocking and class III antiarrhythmic properties. To assess its efficacy in terminating supraventricular tachyarrhythmias (SVT), intravenous S at 1.0 - 1.5 mg/kg was administered in 10 minutes to 23 patients (pts) during electrophysiologic studies. 12 pts manifested orthodromic atrioventricular reciprocating tachycardia (AVRT), 6 pts atrioventricular nodal reentrant tachycardia (AVNRT), 3 pts atrial flutter-fibrillation (AF) with ventricular preexcitation and 2 pts atrial tachycardia (AT). In 5 ± 3 minutes, S terminated SVT in 15 (65%) of total 23 pts -- 10/12 pts with AVRT, 4/6 pts with AVNRT, 0/3 pts with AF and 1/2 pts with AT. In the 8/23 (35%) pts in whom SVT could not be terminated, S slowed the ventricular rate of SVT by 25% (from 168 ± 40 to 125 ± 39 beats/min, $p<0.02$). Antiarrhythmic properties of S could be accounted for by S-induced prolongation of effective refractory periods of atrium, ventricle, atrioventricular node and accessory pathway (+16%, +19%, +19%, and +12%, respectively). During S infusion, 1 pt experienced transient shortness of breath but none developed significant hypotension. Thus, we conclude that intravenous S is a safe and effective agent for acute treatment of SVT of various mechanisms, and is useful in controlling the ventricular rate of AF with ventricular preexcitation by virtue of its depressive action on both accessory pathway and atrioventricular node.