Adverse Hemodynamic Effects of Antiarrhythmic Drugs in Congestive Heart Failure

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Patients with congestive heart failure present a variety of unique therapeutic challenges. One of the more important of these challenges is the treatment of arrhythmias. Patients with congestive heart failure have a high incidence of supraventricular and ventricular arrhythmias, both symptomatic and asymptomatic.1-5 About 40% of deaths in patients with congestive heart failure are sudden and presumed to be the result of an acute arrhythmia.1-3,6-10 Patients with congestive heart failure with ventricular arrhythmia (either symptomatic or asymptomatic) have a higher risk of arrhythmic death than those without ventricular arrhythmia.2,4,5 Therefore, consideration of antiarrhythmic therapy is frequently required in these patients. Unfortunately, there is now increasing evidence that patients with congestive heart failure are more likely to experience serious adverse effects from antiarrhythmic therapy than patients without congestive heart failure. Among the more important of these adverse effects are the induction or aggravation of serious ventricular arrhythmias (proarrhythmic effect)11 and impairment of cardiac contractile function.

Although the potential deleterious hemodynamic effects of disopyramide12 and flecainide13-15 are well known, such effects have received less attention for many other antiarrhythmic agents. Most studies of the effects of antiarrhythmic agents on hemodynamic or left ventricular function have been in patients without congestive heart failure and with mild or no left ventricular dysfunction. Many studies have used noninvasive techniques that may not be sufficiently sensitive to detect a clinically significant negative inotropic effect. Few studies have directly compared one antiarrhythmic agent with another in a randomized trial. The study by Gottlieb and colleagues16 in this issue of Circulation is a direct comparison of immediate hemodynamic changes in a randomized trial of encainide, procainamide, and tocainide in patients with severe congestive heart failure.

Conclusions of the Present Study

Twenty-one patients with refractory congestive heart failure (New York Heart Association functional class III or IV) due to severe left ventricular dysfunction (ejection fraction, less than 0.40; mean, 0.21) were studied after administration of single oral doses of encainide (50 mg), tocainide (600 mg), or procainamide (750 mg). Hemodynamic changes were measured by right heart catheterization 1-2.5 hours after the dose was administered. There were equivalent drops in cardiac index (17-18%) and significant increases in systemic vascular resistance (11-17%) with each of the three drugs. Mean arterial pressure fell with procainamide (6%) but not with encainide or tocainide. Left ventricular filling pressure increased significantly with tocainide and encainide but fell (insignificantly) with procainamide. The investigators concluded that all three drugs may adversely affect left ventricular function in patients with heart failure but that this adverse effect appears to be more severe with encainide or tocainide than with procainamide.

Mechanisms of Hemodynamic Effects

The mechanisms of the hemodynamic effects of antiarrhythmic agents are complex and not fully understood. The hemodynamic changes are highly dependent on the nature of the study (intact organism or isolated preparation), the underlying level of myocardial function, the adrenergic state of the subjects, the rate and route of drug administration, and concomitant therapy.17 For example, three studies in isolated preparations in two species have shown that procainamide has a positive inotropic effect at clinically used drug concentrations.18-20 The study by Austen and Moran18 is particularly instructive, because decreased contractility and systemic pressure were seen only when procainamide was given into the systemic circulation of a canine preparation.
in which the central and systemic circulations were separated. When procainamide was given into the central circulation, increases in contractility and central aortic pressure were seen. These findings indicate that some of the deleterious hemodynamic effects of procainamide may be the result of vasodilation and decreased left ventricular filling. The small decrease in left ventricular filling pressure in the study by Gottlieb et al may be consistent with this hypothesis.

**Limitations of the Present Study**

Several limitations to the present study need to be kept in mind. The rate at which a drug is administered and the time at which the hemodynamic effects are measured can clearly affect the results. Jawad-Kanber and Sherrod observed a significant 12% decrease in cardiac index at the end of a 10-minute infusion of 500 mg procainamide. On the other hand, Burton and colleagues administered procainamide more slowly (100 mg in 2 minutes followed by 20 mg/min in 20–25 minutes) and found no change in cardiac index. In clinical practice, antiarrhythmic therapy is usually initiated at smaller doses than those used in the study by Gottlieb et al.16

In the present study, hemodynamic changes were measured only once after drug administration, and measurement was timed to be at peak drug level. Several studies have shown that the reductions in cardiac output after intravenous administration of procainamide or tocainide are transient. The high incidence of worsening of congestive heart failure in patients receiving encainide (six of 21) or tocainide (seven of 21) must be viewed in light of the relatively high single-dose administration and the absence of blinding or a placebo group. Congestive heart failure occurred or worsened with a surprisingly high frequency (24%, grade 2 or 3) in the Cardiac Arrhythmia Pilot Study but was not significantly different between patients receiving placebo and those receiving encainide.15

**Conclusions**

The present study is particularly useful because it is the first to compare the hemodynamic effects of several antiarrhythmic agents by use of invasive techniques in patients with severe congestive heart failure due to left ventricular dysfunction. The investigators' caution regarding the use of these drugs in patients with severe congestive heart failure is appropriate. Given the recent report of the Cardiac Arrhythmia Suppression Trial showing increased mortality with the use of flecainide and encainide in the treatment of asymptomatic ventricular arrhythmia after myocardial infarction, the increased risk of proarhythmic events, and given the significant deleterious hemodynamic effects reported by Gottlieb and colleagues, the conclusion to limit antiarrhythmic therapy to patients with life-threatening or significantly symptomatic arrhythmias is inescapable, at least until there is randomized trial evidence that suppression of asymptomatic or mildly symptomatic arrhythmias will prolong life.

On the other hand, there are numerous other reports documenting relatively mild or no hemodynamic deterioration as well as a long record of clinical experience indicating a low incidence of induction or exacerbation of congestive heart failure, particularly with procainamide. Therefore, there should be little hesitation in initiating antiarrhythmic therapy in patients with life-threatening arrhythmias or symptomatic arrhythmias. In many patients, procainamide would be an appropriate first choice.

**References**


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