Flecainide Acetate for Long-term Prevention of Paroxysmal Supraventricular Tachyarrhythmias

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Paroxysmal supraventricular tachycardias (PSVTs) encompass a wide range of rhythm disorders and occur in patients of all ages, both in the absence of and in conjunction with underlying heart disease. For example, the reciprocating tachycardias (i.e., tachyarrhythmias due to reentry within the atrioventricular [AV] node or those utilizing any of several different types of accessory connections) tend to manifest themselves initially in a younger set of patients without clinically apparent underlying structural heart disease. Although these individuals are usually considered to be at relatively low risk for life-threatening complications of antiarrhythmic drug treatment, even a rare severe adverse reaction in this group of patients is tragic. Further, the occurrence of less severe but common side effects in this set of patients can evoke a substantial psychological and economic cost. On the other hand, the primary atrial tachycardias (i.e., atrial fibrillation, atrial flutter, sinus node reentry) more often occur in older patients and/or individuals with overt or subtle degrees of heart disease. 

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these patients, the potential for adverse antiarrhythmic drug reactions during long-term treatment may be expected to be more substantial than in younger, otherwise healthy patients, and both initial treatment selection and follow-up warrant careful consideration.

Currently, treatment options for PSVT patients comprise not only a variety of antiarrhythmic drugs but also an arsenal of surgical and transcatheter ablative techniques, as well as sophisticated implantable antitachycardia devices. Occasionally a combination of treatment modalities may be necessary. Pharmacological therapies, however, continue to predominate, primarily because of their apparent convenience. In particular, physicians have increasingly tended to make use of the expanding number of available new antiarrhythmic agents although these drugs have not typically undergone detailed evaluation documenting long-term effectiveness and safety for PSVT patients. As a result, the use of these drugs for treatment of PSVT has been, for the most part, unaccompanied by a specific approved indication.

In this issue of Circulation, Henthorn et al summarize results of a unique multicenter placebo-controlled crossover trial designed to assess the efficacy and safety of flecainide acetate for control of symptomatic PSVT. The complexity of carrying out studies of this type is evident from the fact that despite participation of 19 medical centers, only 34 patients completed the entire protocol and provided analyzable data. Nonetheless, while the study is not without its limitations, the results are very supportive of the potential value of flecainide in PSVT patients, and the study design provides important direction for future studies evaluating antiarrhythmic drug treatment.

Flecainide in PSVT: Prior Studies

The effectiveness of flecainide acetate for both acute termination of supraventricular tachycardias following intravenous administration and long-term arrhythmia prophylaxis has been the subject of a number of previous studies, although none are comparable in design to the multicenter clinical trial by Henthorn et al. Recently, Anderson et al reviewed many of these previous studies and summarized published findings from 1,371 parenteral and oral flecainide treatment trials in patients with a wide range of supraventricular tachyarrhythmias. Criteria for efficacy varied among investigators. Nonetheless, the overall reported effectiveness of the drug was impressive. Intravenous flecainide was effective for acute tachycardia termination in 601/822 trials (73%), and orally administered drug was efficacious for longer term arrhythmia control in 363/549 trials (66%). However, adverse cardiac effects were reported in 6.9% of cases with proarrhythmic events in 4% and conduction disturbances in a further 2.2%. This is in contrast to the reported absence of adverse cardiac effects in the multicenter study summarized by Henthorn et al. To assess this apparent discrepancy we reexamined, for purposes of this communication, recently published reports from the English- and French-language literature in which the nature of the supraventricular arrhythmia could be ascertained, along with an estimate of subsequent drug effective-
ness and side effects during follow-up.11–14,17–19,21,22 Our findings indicate that flecainide therapy was deemed completely or substantially effective in 74% (29/39) of patients with reentry within the AV node and in 66% (41/62) of patients with reentry utilizing an accessory connection. Anderson et al reported effectiveness rates of 73.5% and 81%, respectively, for these arrhythmias. In cases of primary atrial tachycardia (including atrial fibrillation and flutter) we and Anderson et al found flecainide to have similar reported effectiveness rates (52% and 63%, respectively). Additionally, the rates of reported adverse cardiac (8% and 6.9%) and proarrhythmia (6% and 4%) were comparable in our review and in the examination of the literature by Anderson et al.

Based on these two retrospective analyses of flecainide administration in PSVT patients, the long-term effectiveness of the drug appears to range from 50% to 70% depending on the arrhythmia. Additionally, the risk of clinically significant adverse cardiac effects appears to be small, but is not negligible. For example, the development of ventricular tachycardia has been rare, but nonetheless it has occurred. Similarly, atrial flutter with 1:1 AV conduction and a consequent excessively rapid ventricular response has also been reported.13 Of 53 patients with supraventricular tachycardias treated with flecainide in a report by Haissaguerre et al,13 three exhibited “slow” atrial flutter (230 beats/min) with 1:1 AV conduction during therapy, and one of these patients presented in acute hemodynamic collapse requiring urgent cardioversion. One other patient in the same study developed new onset ventricular tachycardia after 2 months’ exposure to flecainide at 350 mg/day. The latter patient was a 78-year-old male with Wolff-Parkinson-White syndrome being treated for paroxysmal atrial fibrillation. Haissaguerre et al also noted new onset congestive heart failure and episodes of sinoatrial block in their overall experience with the drug.

**Flecainide in PSVT: A Multicenter Study**

The multicenter trial of flecainide acetate in PSVT by Henthorn et al8 not only provides evidence substantiating the efficacy of this drug for suppression of symptomatic supraventricular tachyarrhythmias but provides direction for future studies evaluating other pharmacological therapies for PSVT (i.e., outpatient placebo-controlled crossover design). Additionally, while transtelephonic monitoring has been used widely for diagnostic event recording,24–26 its application in this study as a means of assessing treatment effectiveness is unique (but not without limitations, as discussed below). As a result, the multicenter study was able to establish quite clearly the magnitude of flecainide’s effectiveness for reduction of symptomatic tachycardia episodes over an 8-week period (8 episodes with flecainide versus 29 episodes with placebo, p<0.001) as well as its capability to prolong symptomatic tachycardia–free periods (>55 days with flecainide versus 11 days with placebo, p<0.001). Further, the authors were able to distinguish the frequency with which side effects are associated with flecainide treatment (22/35 [63%] patients with flecainide versus 13/36 [36%] patients with placebo).

Several limitations of the multicenter study merit highlighting. First, by virtue of its reliance on transtelephonic event recording, the study was only able to address drug efficacy with respect to symptomatic tachyarrhythmias. Although eliminating the latter may be the most important goal to be achieved, it is nonetheless true that occurrence of slower tachycardias during the active drug phase may have gone undetected, resulting in an overestimate of flecainide’s effectiveness. The latter concern is substantiated by the fact that in those cases in which symptomatic episodes were recorded during flecainide administration, the tachycardia rates were significantly slower than during placebo phase (143±12 beats/min while taking flecainide versus 178±12 beats/min while taking placebo, p<0.02). Second, transtelephonic monitoring does not permit quantitative assessment of proarrhythmic events (e.g., increased frequency of ventricular or atrial ectopy, or nonsustained ventricular tachycardia) that may have been asymptomatic during the 8-week study period but might have important long-term implications. Third, because the study group was relatively young (mean age of the 34 analyzed patients, 50±15 years) and for the most part without prior history of myocardial infarction (no patients), cardiomyogal (four patients), or ventricular ectopy (two patients), the patient population for whom the results of the study are pertinent must be similarly restricted. Additionally, several patients were excluded from the chronic phase of the study because of a suspected “proarrhythmic” event during administration of intravenous flecainide (two of the original 51 patients [4%]). Consequently, the number of potential “proarrhythmia-susceptible” patients in the chronic oral drug phase may have been diluted to some extent.

A fourth limitation of the study is a lack of assessment of the electrophysiological substrate for arrhythmia. As a result, potentially useful insights into the relative merits of the drug under different conditions are lacking. Presumably this aspect of the study design was considered appropriate based on the argument that PSVT patients commonly undergo empirical treatment before electrophysiological study is considered. However, as noted above, previous studies of flecainide use in PSVT patients have reported infrequent but disconcerting adverse cardiac effects.13,17–23,27 Such occurrences were fortunately absent in the multicenter trial by Henthorn et al,8 perhaps in part because of careful patient selection (e.g., because of young age and/or absence of heart disease). Nonetheless, it might be reasonably argued that the risks of treatment with flecainide (and perhaps with other comparable membrane-active antiarrhythmic drugs as well) for arrhythmias, which are more often a life-style than a life-threat-
ening problem, are sufficiently great (compared, for example, to treatment with β-adrenergic blockers or calcium channel blockers) to warrant both examining therapeutic alternatives (see below) and ascertaining potential drug effectiveness by programmed electrical stimulation. Clearly, a subset of the investigators thought that obtaining more detailed electrophysiological evaluation was valuable, in that 16 patients underwent such study. Although not without potential adverse consequences of their own, essentially curative surgical and transcatheter treatment procedures as well as effective implantable antitachycardia devices for many forms of PSVT are treatment alternatives for selected individuals. The empirical use of membrane-active antiarrhythmic drugs without examination of the treatment options evident after complete electrophysiological assessment is a questionable strategy.

A final concern regarding interpretation of the results of the multicenter trial by Henthorn et al. is the duration of the study (only 8 weeks), considering the usual need for obtaining therapeutic effectiveness without troublesome side effects over a time period of many years. This concern is especially pertinent to younger patients, who may compose a substantial portion of potential treatment candidates, because they are at least in their younger years at lower risk for proarrhythmic or adverse hemodynamic effects. In this regard, the recently reported findings of Wiseman et al., in which flecainide treatment of a wide variety of arrhythmias appeared to be well tolerated during a 7.3 ± 9.4 month follow-up, may be reassuring. In this retrospective analysis of findings in 169 patients, flecainide used alone or in combination was reported to have an overall success rate of 73 percent, with only three possible proarrhythmic events noted (two of the three events occurring in patients being treated for ventricular tachyarrhythmias, and one event occurring during therapy for atrial fibrillation). Additionally, in the report by Sihm et al., most apparent proarrhythmic events tended to occur early after initiation of treatment. Thus, among 100 patients (age range, 30–87 years) being treated with parenteral or oral flecainide for paroxysmal atrial flutter or fibrillation, seven of the nine adverse arrhythmogenic events reported occurred within 1–5 days of treatment onset (asystole/bradycardia, two; ventricular tachycardia, two; ventricular fibrillation/sudden death, three). Of note, the two late arrhythmogenic effects were both bradycardias (sinus arrest). Unfortunately, it is impossible to determine from this study by Sihm et al. the precise number of proarrhythmic events occurring among the 28 patients who were ultimately discharged on oral flecainide for tachycardia prophylaxis. However, it appears likely that the two late bradycardia events and at least one episode of ventricular tachycardia (total, three of 28 [11%]) can be considered to have occurred in this setting.

Implications of Cardiac Arrhythmia Suppression Trial Findings

The potential role of flecainide and similar type 1C antiarrhythmic agents (e.g., encainide) in PSVT patients cannot be divorced from the recently published findings of the Cardiac Arrhythmia Suppression Trial (CAST). Although this study was directed toward arrhythmia prevention in patients with ventricular ectopy and ischemic heart disease, the PSVT population often includes patients with these disorders (especially among those being treated for primary atrial tachyarrhythmias).

In essence, CAST findings revealed an approximately 3.6-fold and 2.5-fold excess in arrhythmic deaths/cardiac arrests and total mortality, respectively, in flecainide/encainide-treated patients and those taking placebo. Further, while the total risk of arrhythmic death/cardiac arrest was clearly higher among patients with poorer left ventricular function (ejection fraction <30%: 9.5% with drug versus 3.6% with placebo: ratio, 2.7:1), the relative impact of drug was nonetheless disturbingly high in the patients with better LV function (ejection fraction ≥30%: 3.7% with drug versus 0.8% with placebo: ratio, 4.5:1). Additionally, compared with patients taking placebo, the frequency of arrhythmic death/cardiac arrest in flecainide/encainide-treated patients exhibited an approximate 5.1-fold excess in patients with an additional prior myocardial infarction, and a 7.2-fold excess among patients with ≥50 PVCs/hr.

The mechanisms for the apparent adverse effects of flecainide and encainide in CAST remain the subject of considerable discussion and analysis. Nonetheless, the conclusions ultimately drawn from the CAST experience will certainly color drug selection in treatment of PSVT patients as well. This will be the case even in the absence of ischemic heart disease in most PSVT patients. For example, our own experience includes the development of unanticipated cardiovascular collapse in two flecainide-treated patients without coronary disease. In one young individual with congenital heart disease being treated with flecainide to prevent paroxysmal atrial flutter, drug therapy was associated with a prolonged asystolic cardiac arrest initiated by an episode of atrial flutter with 1:1 AV conduction. The second patient was a middle-aged man, being treated for paroxysmal atrial fibrillation in the absence of apparent underlying cardiac disease. He suffered a sudden undocumented cardiac death. Autopsy examination of the second patient was unrevealing. These unfortunate outcomes are not unique, given the occurrence of new onset of ventricular tachyarrhythmias and development of 1:1 AV conduction during atrial flutter reported previously in both adults and children treated with flecainide. Consequently, despite the convincing efficacy data presented, we believe that the multicenter study has probably to some extent underes-
timated the risks associated with use of type 1C antiarrhythmic agents in PSVT patients.

**Recommendations**

Flecainide acetate is probably the most thoroughly evaluated antiarrhythmic drug for use in PSVT. Its effectiveness in suppression of supraventricular tachyarrhythmias is evident from the extensive literature on the subject as well as from the findings of the multicenter trial summarized by Henthorn et al.\(^9\) Our own experience and those of others\(^10-22,27\) have for the most part been similarly favorable. However, the risks of antiarrhythmic drug therapy in general are becoming increasingly apparent, and the potential adverse effects of empirical drug treatment should not be overlooked. Consequently, because safety is a major concern, \(\beta\)-adrenergic and/or calcium channel blocking drugs would seem to be appropriate first-line agents for PSVT patients, with cardiac glycosides being an available but usually less effective alternative for patients without ventricular preexitation. In the event that additional therapy is needed, careful screening would be prudent in order to exclude use of type 1 (especially type 1C) antiarrhythmic drugs in individuals with clinical features paralleling those of the CAST high-risk group.\(^28\) Indeed, it would be reasonable to avoid these agents entirely in patients with asymptomatic or mildly symptomatic arrhythmia. Further, it would seem reasonable at this stage of the decision-making process to take advantage of electrophysiological studies in an attempt to establish the diagnosis unequivocally, assess the tachycardia mechanism(s), and define the treatment options.

With this information, symptomatic patients can be more fully informed of their condition and can participate in decisions regarding their care. However, when a membrane-active agent is chosen, flecainide acetate appears to be a well studied and very effective contender, with adverse consequences probably no worse than most other antiarrhythmic agents at our disposal.

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**References**


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