CLINICAL ELECTROPHYSIOLOGIC EFFECTS OF FLECAINIDE ACETATE

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Cellular Electrophysiology

The cellular electrophysiology of flecainide, as studied on isolated preparations of canine and mammalian cardiac muscle, has led to an understanding of its clinical electrophysiology. The cellular effects of the drug have been investigated in detail by Cowan and Vaughan Williams [1] and Iked et al. [2]. It has no effect on the resting membrane potential. The most striking effect is a dose dependent decrease of the maximum velocity of depolarization ($V_{\text{max}}$) in various isolated cardiac tissues [1, 2]. This action correlates with a potent inhibitory action on the fast sodium current [3]. The duration of the action potential of ventricular muscle is minimally prolonged while that of the Purkinje fibers is reduced [2]. Flecainide increases the effective refractory period of ventricular muscle in a concentration-dependent manner, the prolongation being more than that of action potential duration, while the effective period of the Purkinje fibers is shortened in low concentrations but unaltered at higher concentrations [2]. Studies on the intact canine heart showed that flecainide causes slowing of conduction, and that this effect occurs predominantly in the His bundle and ventricles [4], an observation that has subsequently been confirmed in human studies [5].

How flecainide is best classified, is still a matter of debate. The main mechanism of its antiarrhythmic action is probably related to its effect on the fast sodium channels, thereby reducing the rate of rise of the action potential and shift of the so-called membrane responsiveness curve to the left. Thus, it has local anaesthetic or “membrane stabilizing” properties on the basis of which it is appropriately classified as a Vaughan Williams’ class 1 drug. According to ef-
flect on action potential duration, Harrison [6] proposed a subclassification of class 1 agents as follows: class 1a drugs, such as quinidine, procainamide, and disopyramide which significantly prolong action potential duration; class 1b drugs such as lignocaine and tocainide which shorten the action potential duration; class 1c drugs such as flecainide, encainide, and similar drugs which have little or no effect on myocardial action potential duration. Clinical experiments by Milne et al. [7] on the effect of various class 1 drugs on repolarization show analogous effects and therefore support the use of this classification. Although, flecainide has been classified as a class 1c drug, several human [8–10] and animal studies [1, 2] have shown a significant increase in refractoriness (atrial and ventricular) and action potential duration (ventricular). However, in some respects it differs from class 1a drugs in that it markedly prolongs conduction (Q-R-S interval duration is increased) and does not significantly slow repolarization (J-T interval is not altered) [11]. Electrophysiologically, it is also distinct from class 1b agents which, unlike flecainide, decrease the action potential duration of Purkinje fibers and ventricular muscle [12]. Furthermore, prolongation of conduction through the His-Purkinje system and myocardium as seen with flecainide is not seen with class 1b agents [13, 14]. It shares most of its electrophysiologic effects with other agents of class 1c, i.e., encainide and lorcaainide [15, 16] with minor differences. Lorcaainide, for example, slightly lengthens Purkinje cell action potential, while encainide has no effect on myocardial action potential duration.

Thus, better understanding of flecainide's electrophysiologic effects and its pharmacologic diversity has made it difficult to precisely classify flecainide, although at present it is best grouped under class 1c.

Clinical Electrophysiology

The clinical electrophysiologic effects of flecainide have been studied mostly by the use of conventional intracardiac recording and stimulation techniques. Most of these data have been obtained after intravenous (rather than oral) drug administration. The usual intravenous dose in adults is 2 mg/kg given slowly over 10 to 15 minutes. The electrophysiologic actions detected using this technique [5, 17] may be categorized as follows:

1. Sinoatrial function.
2. Atrial refractoriness and conduction.
3. Atrioventricular (AV) nodal refractoriness and conduction.
5. His-Purkinje tissue refractoriness and conduction.
6. Ventricular myocardial refractoriness and conduction.
7. Stimulation thresholds.

The antiarrhythmic actions of flecainide have been investigated in relation to

1. Atrial tachycardias, including atrial flutter and fibrillation.
2. Paroxysmal junctional tachycardias.
3. Ventricular tachycardias.

Actions on the Sinus Node

The action of flecainide on sinus node function, as with many other class 1 agents, is most pronounced in patients with sinoatrial disorders [18]. Although flecainide has no major effects on the sinus rate [4, 5, 19], it may prolong derived variables such as sinoatrial conduction time (SACT) and sinus node recovery time (SNRT) [18]. The clinical importance of these effects is not clear but the implication is that patients with important sinoatrial disorders are more susceptible to the effects of the drug [18] and may develop long sinus pauses or sustained bradycardias. The mechanism of this action is not known. However, other drugs with class 1 (Vaughan Williams) properties are also known to aggravate abnormal sinus node function [20, 21].

Action on the Atrium

Intra-atrial conduction time as measured by the P-A interval appears to be prolonged by intravenous flecainide [5, 6]. Atrial refractoriness does not appear to be consistently affected. In one study no change was seen [5] but in two other studies a significant prolongation was noted [18, 22]. The reasons for such a major discrepancy of results is unclear. Oral flecainide has no consistent effect on the atrial refractory period although there is a tendency towards prolongation.

Actions on the Atrioventricular Node

The effective refractory period of the normal AV node is not significantly changed by flecainide in those