The Antifibrillatory Actions of UK-68,798, A Class III Antiarrhythmic Agent

SHAWN C. BLACK, LIGUO CHI, DUN-XUE MU and BENEDICT R. LUCCHESI
University of Michigan Medical School, Department of Pharmacology, Ann Arbor, Michigan
Accepted for publication April 15, 1991

ABSTRACT

The electrophysiologic and antifibrillatory properties of UK-68,798 were studied in vivo in a conscious canine model of sudden coronary death. Electrophysiologic testing was performed on conscious male mongrel dogs (14.5–21.5 kg) 3 to 5 days after surgical induction of an anterior myocardial infarction by occlusion (2 h)-reperfusion of the left anterior descending coronary artery. Compared to saline-treated control animals, UK-68,798 at a dose of 0.9 mg/kg i.v. did not (P = .083) suppress the induction of ventricular tachycardia by programmed electrical stimulation. Six of 12 UK-68,798-treated dogs remained inducible, whereas 10 of 12 vehicle-treated dogs responded to electrical induction of arrhythmia. When compared to predrug inducibility, UK-68,798 significantly (P = .007) reduced the incidence of programmed electrical stimulation-induced ventricular tachycardia. In five of the six dogs inducible after UK-68,798 administration, the cycle length of the induced ventricular tachycardia was prolonged (P = .007) compared to the predrug cycle length.

Heart rate, PR interval and QRS duration were not affected by UK-68,798 administration. The rate-corrected QT interval was prolonged (P < .05) by UK-68,798. The ventricular effective refractory period was increased by UK-68,798 (158 ± 7 msec, predrug vs. 185 ± 7 msec, postdrug). Subsequent to programmed electrical stimulation, a 150 μA anodal current was applied to the luminal surface of the left circumflex coronary artery to induce transient episodes of posterolateral ischemia in response to electrolytic injury of the vessel wall. Sudden death, defined as ventricular fibrillation occurring within 60 min after the onset of posterolateral ischemia, was reduced (P < .05) in UK-68,798-treated dogs as compared to the saline-treated group (33.3% vs. 83.3%). Myocardial infarct size (anterior or posterior) and thrombus mass were not different between UK-68,798 and vehicle groups. The results suggest that UK-68,798, a class III agent, warrants further evaluation as a potential antifibrillatory drug.

Reentry is the electrophysiologic mechanism most likely responsible for the development of serious ventricular arrhythmias observed clinically (Wellens et al., 1976; Josephson et al., 1978; Downar et al., 1988) as well as in experimental animal models (Cardinal et al., 1984; El-Sherif et al., 1981; Wit et al., 1982; Kramer et al., 1985). The initiation and maintenance of a reentrant tachyarrhythmia requires a conduction pathway of sufficient length in which there is a critical relationship between conduction velocity and refactoriness (Han, 1971). Understanding the potential mechanism(s) for the genesis of reentrant ventricular tachyarrhythmias suggests that a selective increase in ventricular repolarization and the associated increase in myocardial refactoriness, with minimal effects on conduction velocity, might suffice to prevent the development of malignant arrhythmias.

The early phase of myocardial ischemia is accompanied by a shortening in the duration of the action potential and a loss of intracellular K+ with its concomitant increase in the extracellular space (Kleber, 1984; Kleber et al., 1987). Evidence suggests that more than one mechanism contributes to myocellular K+ efflux during ischemia. One possible mechanism is a decrease in myocellular ATP concentration during ischemia contributing to the increased K+ efflux by allowing ATP-dependent K+ channels to open (Noma, 1983; Noma and Shibasaki, 1985). There is support for the view that opening of K+ATP channels contributes significantly, although not exclusively, to extracellular K+ accumulation in the first few minutes of ischemia (Wilde et al., 1990). Glibenclamide, a selective inhibitor of the K+ATP channel, possesses antiarrhythmic properties by virtue of its ability to prevent intracellular K+ loss in the early ischemic period (Wollenben et al., 1988; Kantor et al., 1990). Other mechanisms proposed to account for myocellular K+ efflux during ischemia include increased passive K+ efflux and K+ efflux resulting from an ionic shift in response to anion

ABBREVIATIONS: ERP, effective refractory period; IZ, infarct zone; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; NZ, normal zone; QTc, rate-corrected QT interval; RRP, relative refractory period; RVOT, right ventricular outflow tract; TTC, triphenyl tetrazolium chloride; VT, ventricular tachyarrhythmia; PES, programmed electrical stimulation.
Acidosis (Kleber et al., 1987). As demonstrated with glibenclamide, inhibition of myocardial K⁺ loss and its attendant effect of reducing the action potential duration is a potential pharmacologic means of inhibiting ischemia-induced ventricular tachyarrhythmias and ventricular fibrillation. The class III antiarrhythmic drugs dl-sotalol and E4031, which prolong the action potential duration and increase ventricular ERP in the canine heart (Lynch et al., 1984, 1990), have been shown to block a component of the delayed rectifier K⁺ current in guinea pig ventricular cells (Sanguinetti and Jurkiewicz 1990). Thus, it is apparent that inhibition of cardiac potassium channels may be an effective pharmacologic means of controlling arrhythmias and possibly ventricular fibrillation.

UK-68,798 is a new class III antiarrhythmic drug capable of prolonging the action potential duration and ERP in ventricular muscle without altering the maximum upstroke velocity of the membrane action potential (Gwilt et al., 1991). The drug has been shown to increase the ventricular ERP and reduce the incidence of programmed electrical stimulation-induced ventricular tachycardia in anesthetized open-chest dogs with a previous myocardial infarction (Zuanetti and Corr 1991). UK-68,798 has not been shown to be effective at reducing programmed electrical stimulation-induced ventricular fibrillation (Zuanetti and Corr 1991). The purpose of the present investigation was to examine the putative antiarrhythmic actions of UK-68,798 and also to determine possible antiarrhythmic activity of the drug during the onset of posterolateral ischemia in a conscious canine model with a previous myocardial infarction. The results of our investigation suggest that UK-68,798 produces minimal effects on ventricular conduction time while increasing ventricular refractoriness in the postinfarcted heart. The observed electrophysiologic changes are believed to be associated with the ability of UK-68,798 to act as an effective antiarrhythmic agent in a conscious canine model of sudden cardiac death.

Methods

Guidelines for animal research. The procedures followed in this study were in accordance with the guidelines of the University of Michigan University Committee on the use and care of animals. Veterinary care was provided by the University of Michigan unit for laboratory animal medicine. The University of Michigan is accredited by the American Association for Accreditation of Laboratory Animal Care, and the animal care and use program conforms to the standards in "The Guide for the Care and Use of Laboratory Animals (DHEW Publ. No. (NIH) 86–23).

Surgical preparation. Male mongrel dogs (14.5–21.5 kg) were anesthetized with i.v. sodium pentobarbital (6%), 30 mg/kg. The dogs were ventilated with room air by means of a cuffed endotracheal tube and a Harvard respirator. Using aseptic technique, the left external jugular vein was isolated and a cannula inserted. A left thoracotomy was performed between the fourth and fifth ribs, and the heart exposed and suspended in a pericardial cradle. The LAD was isolated at the tip of the left atrial appendage and the LCX was isolated approximately 1 cm from its origin. A ligature was placed around the LAD and a 20-gauge hypodermic needle. The ligature was tied around the artery and the needle, after which the needle was removed, thereby resulting in a critical stenosis of the vessel. The LAD was perfused in the presence of the critical stenosis for a period of 5 min. Ischemic injury of the anterior ventricular myocardium was achieved by a 2 hour occlusion of the LAD by means of a silicone rubber snare. The vessel was reperfused after 2 h in the presence of the critical stenosis. During the period of LAD reperfusion, an epicardial bipolar electrode (1 mm silver posts, 3 mm interelectrode separation) was sutured to the left atrial appendage for subsequent atrial pacing. A bipolar plunge electrode (25-gauge stainless steel, 5 mm long, 3 mm separation) was sutured into the interventricular septum, adjacent to the occlusion site and overlying the RVOT. Two similar stainless steel, bipolar plunge electrodes were sutured to the left ventricular wall: one in the distribution of the LAD distal to the site of occlusion (IZ) and the second in the distribution of the LCX (NZ). A 30-gauge silver-coated copper wire electrode was passed through the wall and into the lumen of the LCX and secured by suture to the adjacent surface of the heart. Silver disc electrodes were implanted s.c. for ECG monitoring. The surgical incision was closed and the animals were allowed to recover. Routine antibiotic (10 mg/kg ampicillin s.c.) was given daily for 3 or 4 days postoperatively.

Electrophysiologic study and programmed electrical stimulation. Programmed electrical stimulation was performed between days 3 and 5 after the surgical induction of the anterior myocardial infarction by occlusion/reperfusion of the LAD. Animals were studied while conscious and unsedated. Heart rate, ECG intervals and electrophysiologic parameters were determined immediately before initiating programmed electrical stimulation testing. ECG intervals were measured during sinus rhythm (paper speed 100 mm/sec). A corrected QT interval (QTc = QT interval in msec/[R-R interval in sec]0.5) was determined during sinus rhythm, whereas a paced QT interval (QTp) was determined during atrial pacing at 2.5 Hz (heart rate = 150 beats/min). The ventricular excitation thresholds and the refractory periods, as well as NZ and IZ activation delays and conduction times, were recorded during atrial pacing at 2.5 Hz. The ventricular excitation threshold (determined in the region of the RVOT) was defined as the minimum voltage required to produce a conducted ventricular complex (V2) with an S2 stimulus duration of 4 msec delivered 300 msec after the R-wave of the lead II ECG. The ventricular ERP in the region of the RVOT was the longest R-S2 coupling interval at which a 2 × threshold stimulus of 4-msec duration failed to elicit a conducted ventricular impulse (V2).

Activation delay, i.e. the duration of electrical activity on the local ventricular electrogram filtered at 50 and 500 Hz, in the NZ and IZ was measured on a Tektronix model 5111 oscilloscope (Tektronix Inc., Beaverton, OR). Conduction times were measured from the interval between the paced ECG Q-wave and the maximal deflection of the local ventricular electrogram (Q-EG) as measured on oscillographic paper at a speed of 200 mm/sec. The ventricular excitation threshold, RRP and ERP in the NZ and IZ, was determined by the construction of ventricular strength-interval curves. Using a modification (Lynch et al., 1986, 1988; Nelson et al., 1988) of the method of Michelson and coworkers (Michelson et al., 1980). During atrial pacing at 2.5 Hz, a timed extrastimulus (S2) was delivered 300 msec after the preceding R-wave of the ECG (S1), and the minimum amperage was determined for eliciting a ventricular response. The S1-S2 coupling was decreased incrementally until the same current failed to produce a conducted response, at which stage the current intensity was increased to the point where a ventricular response was achieved. This sequence was repeated until a coupling interval was determined at a current of 4 mA (Michelson et al., 1980). The ERP was defined as the longest S1-S2 interval which failed to produce a ventricular response. The RRP was defined as the longest S1-S2 coupling interval along the strength-interval curve at which the current required to produce a ventricular response increased by more than 0.025 mA for a 1 msec change in coupling interval (Nelson et al., 1988, Michelson et al., 1980).

The pacing protocol for programmed ventricular stimulation was identical to that used by this laboratory in previously reported studies (Lynch et al., 1984; Nelson et al., 1988). Premature ventricular stimuli (4 msec duration, 2 × threshold) were introduced into the region of the RVOT by means of a Grass model S-88 stimulator and a Grass model SIU-5 stimulus isolation unit. The extrastimuli were triggered from the R-wave of the ECG (S1) and the S1-S2 coupling interval decreased from 350 msec until ventricular refractoriness. At this point double and triple ventricular extrastimuli were introduced during sinus rhythm. The observed electrophysiologic changes are believed to be associated with the ability of UK-68,798 to act as an effective antiarrhythmic agent in a conscious canine model of sudden cardiac death.
at S2-S3 and S2-S3-S4 coupling intervals of 182, 167, 154, 142, 133 and 125 msec. VTs were defined as nonsustained if, by using the protocol described previously, five or more repetitive ventricular responses were initiated reproducibly, but terminated spontaneously. VTs were defined as sustained if they persisted for at least 30 sec or, in the event of hemodynamic compromise, they required ventricular burst pacing for their termination. If VT degenerated into ventricular fibrillation, the animal was excluded from the study to avoid the potentially confounding influence of occasionally prolonged resuscitative efforts on the outcome of the second phase of the investigation. Animals responding with less than five nonstimulated complexes during the entire protocol were designated as noninducible. Previous work has shown that this method fails to produce ventricular dysrhythmias in sham-operated animals without previous myocardial ischemic injury (Patterson et al., 1982).

Conscious canine model of sudden cardiac death. Upon completion of the post-treatment stimulation protocol, a direct anodal current of 150 μA was applied to the intimal surface of the LCX using a 9 V nickel-cadmium battery and 250,000 ohm variable resistor. The previously implanted intracoronary silver-coated copper wire electrode was attached to the anode, while a s.c. disc electrode served as the cathode. Lead II of the ECG was recorded for 30 sec at preset intervals every 15 min by a programmable FM cardio cassette recorder. After 24 h of constant anodal current or the development of ventricular fibrillation, the heart was excised and any thrombus in the LCX was removed and weighed. The heart was sectioned transversely and incubated for 15 min at 37°C in a 0.4% solution of TTC. Anterior and posterolateral areas of infarcted myocardium were identified by the failure to reduce TTC enzymatically to a brick-red formazan precipitate. Infarct mass in the LAD region (surgically induced) and the LCX region (due to occlusive thrombus) was quantified gravimetrically and expressed as a percentage of total left ventricular mass. A review of the FM tape recordings on the cardio cassette provided information regarding the time of onset of ischemia (as assessed by the appearance of ventricular ectopy and/or ST segment changes), the time from the onset of ischemia to lethal arrhythmia and the change in heart rate upon LCX ischemia.

Experimental protocol. The experimental protocol used in this study is represented by figure 1. Two groups of postinfarction dogs were subjected to programmed stimulation testing. Dogs assigned to the vehicle control group were subjected to electrophysiologic testing and programmed stimulation before and after treatment with 0.9% sodium chloride solution at pH 7.4. After determination of baseline electrophysiologic values and pretreatment programmed stimulation testing, dogs in the experimental drug treatment group were subjected to repeat programmed stimulation testing 30 min after administration of the first dose of UK-68,798. A single i.v. dose (0.9 mg/kg) was given as a continuous i.v. infusion for 15 min. The same dose of UK-68,798 was administered every 5 h. After post-treatment programmed stimulation testing, dogs in the vehicle and drug treated groups were entered into the protocol for sudden cardiac death.

All dogs in this evaluation were assigned randomly to their respective treatment groups before pretreatment electrophysiologic determinations were conducted. Only dogs that were susceptible to the reproducible induction of nonsustained or sustained ventricular tachydysrhythmias by pretreatment programmed stimulation were acceptable for inclusion in the study protocol.

Drugs. UK-68,798 (fig. 2) was provided as the free base (MW 441.6) and prepared in 0.1 N hydrochloric acid. The drug was freely soluble in dilute acid media and was prepared immediately before administration.

Statistical analysis. For all evaluations, data are expressed as the mean ± S.E.M. Pre- and post-treatment values within a given treatment group were compared by the paired Student's t test. Differences between treatment groups were analyzed by unpaired Student's t test. Nominal data dealing with the incidence of inducibility by programmed electrical stimulation and ventricular fibrillation were analyzed using Fisher's Exact test. All data were analyzed using a Macintosh computer (Cupertino, CA) and Statview 512+ software (BrainPower Inc., Calabas, CA). For all comparisons, P < .05 was the criterion for statistical significance.

Results

A total of 43 dogs were used in this study. Nine dogs died during surgery or within the first 3 days after surgery. Thirty-four conscious dogs were subjected to programmed ventricular stimulation 3 to 5 days after surgical induction of an anterior myocardial infarction. Six dogs were noninducible before treatment and were entered into an alternate study. Two dogs responded to programmed stimulation with ventricular fibrillation before experimental intervention and were not resuscitated. The remaining 26 dogs, randomly allocated to the vehicle and UK-68,798 treatment groups, responded to pretreatment programmed stimulation with repeatable nonsustained or sustained VTs. Two dogs were excluded from the analyses due to a technical problem with the LCX electrode discovered at the end of experiment. The electrophysiologic, antiarrhythmic or antifibrillation responses of the two groups of animals form the basis of this report.

Programmed electrical stimulation. The administration of UK-68,798, (0.9 mg/kg i.v.) suppressed the induction of VT by programmed stimulation in six of 12 dogs. Two of 12 dogs were noninducible after saline administration. There was no difference (P = .083, by Fisher's Exact test) between the UK-68,798 and saline treated groups with respect to induction of nonsustained or sustained VTs. Two dogs were excluded from the analyses due to a technical problem with the LCX electrode discovered at the end of experiment. The electrophysiologic, antiarrhythmic or antifibrillation responses of the two groups of animals form the basis of this report.

![Fig. 1. The experimental protocol for the study of UK-68,798 in the postinfarcted conscious canine model of sudden cardiac death.](image)

![Fig. 2. Chemical structure of UK-68,798.](image)
inducible after UK-68,798, the cycle length of the induced tachyarrhythmia was significantly increased (P = .007). In these five dogs, the cycle length of the induced ventricular tachycardia increased from 171 ± 23 msec (mean ± S.E.M., n = 5) before UK-68,798 to 201 ± 19 msec after the drug.

Electrophysiologic responses. The effects of UK-68,798 and vehicle on heart rate, PR interval, QRS duration, QTc and QTp intervals are shown in Table 1. UK-68,798 did not influence the heart rate, PR interval or QRS duration. The QTc interval was increased significantly by UK-68,798 treatment. Unexpectedly, the QTc interval of vehicle-treated animals also was increased. UK-68,798 treatment increased the ventricular ERP in the region of the RVOT (fig. 3). The effect of UK-68,798 on electrophysiologic parameters in the normal and infarcted regions of the left ventricle are shown in Table 2. The drug increased the ERP in the infarcted region of the left ventricle, and also increased the RRP in the noninfarcted region of the left ventricle. UK-68,798 did not alter ventricular excitation threshold, activation delay or conduction times in either normal or infarcted regions. A decrease in the RRP of the normal zone was observed after vehicle administration, however, no other electrophysiologic parameter or ECG interval was affected.

Spontaneous ventricular ectopic activity. Spontaneous ventricular ectopic activity was observed in seven of 12 (58%) UK-68,798-treated dogs. The arrhythmias were transient in nature: they began approximately 10 min after drug infusion and terminated spontaneously within 60 min. The episodes of ventricular ectopy were suppressed readily by atrial pacing at a rate of 150 beats/min. episodes of spontaneous ventricular ectopy were not observed in vehicle-treated animals.

Conscious canine model of sudden cardiac death. Immediately upon completion of the electrophysiologic evaluations in each animal, an anodal current of 150 μA was delivered to the intimal surface of the LCX of UK-68,798 and vehicle-treated dogs. The application of an anodal current to the intimal surface of the LCX resulted in intimal injury, gradual thrombus formation and the subsequent development of posterolateral myocardial ischemia. At autopsy it was determined that the tip of the wire inserted into the LCX had failed (the wire was either broken or outside of the vessel) in two dogs from the UK-68,798 group. Neither intimal surface injury nor thrombus was evident in these dogs and they were excluded from the protocol. The responses of the vehicle and UK-68,798-treated groups to the development of posterolateral ischemia at a site remote from the surgically induced myocardial infarction are summarized in Table 3 and fig. 4. The time to the development of ECG evidence of posterolateral ischemia (ST segment change and/or rhythm disturbances) did not differ between the vehicle and UK-68,798 groups (172 ± 30 and 206 ± 42 min, respectively). The reflex tachycardic response to posterolateral ischemia, the LCX thrombus mass and myocardial infarct size (anterior and posterior) were not different between the vehicle- and UK-68,798-treated groups (Table 3). A posterior infarct could not be visualized with the triphenyl tetrazolium method in 10 of 12 vehicle-treated dogs due to the acute development of ventricular fibrillation after the onset of the posterolateral ischemia. Ventricular fibrillation within 1 h of the onset of regional ischemia provides insufficient time for the development of irreversible cellular injury detectable by the histochemical reaction of cellular dehydrogenases with the tetrazolium salt. Quantitation of the infarct mass within the posterolateral region of the left ventricle was successful in eight UK-68,798 treated animals.

A survival curve showing the effect of UK-68,798 and vehicle on sudden cardiac death and 24-h mortality is shown in figure 4. In the vehicle-treated group, 10 of 12 dogs (83%) developed ventricular fibrillation within 60 min (sudden cardiac death) of the ECG manifestation of posterolateral ischemia, determined by alterations in the lead II ECG recording. Pretreatment with UK-68,798 provided significant protection against the development of ventricular fibrillation occurring in response to posterolateral ischemia in postinfarction dogs. In the UK-68,798-treated group, only four of 12 dogs (33%) died of ventricular fibrillation within the first 60 min of LCX ischemia. The drug significantly reduced the number of dogs exhibiting sudden death within the first hour of regional ischemia as compared to the vehicle-treated group (P = 0.016, Fisher's Exact test). Three UK-68,798-treated dogs died between 1 and 3 h from the onset of posterolateral ischemia. A 24-h cumulative mortality of 58% (7 of 12 dogs) indicated that UK-68,798 treatment protected against delayed death (vs. 92% (11 of 12) of the vehicle-treated group), but this reduction did not reach statistical significance (P = 0.071 by Fisher's Exact test).

**Discussion**

The results of this study demonstrate that UK-68,798, a putative class III antiarrhythmic agent, possesses antiarrhythmic and antifibrillatory effects in a conscious canine model of sudden cardiac death. As demonstrated previously (Patterson *et al.*, 1982; Wilber *et al.*, 1985), the animal model used in this study shows a predictive relationship between baseline inducible ventricular arrhythmias and susceptibility to the development of lethal arrhythmias in response to a superimposed ischemic event in a region remote from the infarcted related artery. Sudden death in our animal model is defined as death due to ventricular fibrillation within 1 h from the onset of posterolateral ischemia. Electrocardiographic evidence of regional ischemia is manifest by ST segment change as either

**TABLE 1**

The effects of UK-68,798 and vehicle on heart rate and electrocardiographic intervals

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>UK-68,798</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>124 ± 7</td>
<td>118 ± 5</td>
</tr>
<tr>
<td>PR interval (msec)</td>
<td>99 ± 4</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td>60 ± 2</td>
<td>62 ± 2</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>299 ± 7</td>
<td>337 ± 8a</td>
</tr>
<tr>
<td>QTp (msec)</td>
<td>207 ± 5</td>
<td>221 ± 9</td>
</tr>
</tbody>
</table>

Mean ± S.E.M.

* P ≤ .05, compared with pretreatment in the same group by Student's paired t-test.

a P ≤ .01, compared with pretreatment in the same group by Student's paired t-test.

* P ≤ .05, compared with corresponding vehicle group.
The effects of UK-68,798 and vehicle on the ventricular ERP of the postinfarcted conscious canine (*significantly different from predrug, P < .05).

![Graph showing the effects of UK-68,798 and vehicle on ventricular ERP.](image)

- Significant with paired t-test within group. 1 Significant with unpaired t-test between groups.

**Fig. 3.** The effects of UK-68,798 and saline vehicle on the ventricular ERP of the postinfarcted conscious canine (*significantly different from predrug, P < .05).

Depression or elevation from baseline and often associated with the appearance of coupled ectopic complexes. We previously demonstrated that the superimposition of an ischemic episode in a region remote from the infarct-related vessel results in ventricular fibrillation within 1 h from the onset of regional myocardial ischemia. Therefore, the critical time point in the experimental protocol relates to the early period after onset of ischemia when ventricular fibrillation is most likely to be the terminal event, as opposed to a delayed death in which “pump failure” is the most likely cause. The latter mechanism of death is related to the development of a second myocardial infarct in the posterolateral region of the heart that further compromises cardiac function. The observations with UK-68,798 are in agreement with the results obtained with other class III drugs such as CK3579 and sematilide, E4031 (Lynch et al., 1984, 1990; Patterson et al., 1981). In the current study, UK-68,798 protected against PES-induced ventricular arrhythmias by 50%, which was significantly lower than the incidence of predrug inducibility. Clinically, the ability of a drug to suppress PES-induced arrhythmias has been suggested to be indicative of a better prognosis for therapeutic success (Rahimtoola et al., 1987), however, others have provided evidence to the contrary (Kim et al., 1987). More recently, the CAST study demonstrated that although encainide and flecainide were effective in suppressing asymptomatic and mildly symptomatic ventricular arrhythmias, these drugs did not protect against sudden cardiac death and actually increased the risk of having a lethal arrhythmic event. In this regard it is relevant to note that experimentally, flecainide failed to prevent PES-induced ventricular tachycardia, and also failed to prevent sudden cardiac death in a conscious canine model in the presence of previous anterior myocardial infarction (Kou et al., 1986). An increased mortality associated with pharmacologic management of cardiac arrhythmias is not limited to the treatment of ventricular arrhythmias. Although effective in suppressing atrial fibrillation, the risk of sudden death associated with quinidine in this setting is approximately 3 times that of untreated patients (Coplen et al., 1990). Therefore, the significant reduction in sudden cardiac death due to ventricular fibrillation associated with UK-68,798 treatment may be a more relevant end point in the preclinical evaluation of this drug than its ability to prevent PES-induced ventricular tachycardia.

Adverse drug reactions (i.e., pulmonary toxicity in 1-13% of patients receiving amiodarone; Mason, 1987) can limit the success of antiarrhythmic therapy. Additionally, proarrhythmic effects constitute an additional risk associated with drug treatment of ventricular arrhythmias (Velebit et al., 1982). In the current study, UK-68,798 induced spontaneous ventricular ectopic activity in seven of 12 dogs (58%) treated with the drug. The arrhythmic episodes were transient and sporadic in nature. The spontaneous arrhythmias essentially ceased before initi-
TABLE 3

Summary of results of UK-68,798 and vehicle in the sudden death protocol

<table>
<thead>
<tr>
<th></th>
<th>UK-68,798</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to ischemia (min)</td>
<td>172 ± 30</td>
<td>206 ± 42</td>
</tr>
<tr>
<td>Change in HR (beats/min)</td>
<td>14 ± 7</td>
<td>18 ± 10</td>
</tr>
<tr>
<td>Myocardial Infarct Size (% left ventricle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>23.8 ± 1.1</td>
<td>25.7 ± 1.1</td>
</tr>
<tr>
<td>Posterior*</td>
<td>25.6 ± 3.7</td>
<td>31.9</td>
</tr>
<tr>
<td>Thrombus mass (mg)</td>
<td>19.6 ± 3.3</td>
<td>13.6 ± 2.1</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden (60 min)</td>
<td>33.3%**</td>
<td>83.3%</td>
</tr>
<tr>
<td>Total 24 hour</td>
<td>58.3%*</td>
<td>91.6%</td>
</tr>
</tbody>
</table>

*Expressed as mean ± S.E.M.

**Only available in animals not dying within 60 min of LCX ischemia, for UK-68,798, n = 8, vehicle, n = 2 (the posterior infarct from one of two animals was undetectable).

**p = .071 compared with corresponding vehicle group by Fisher’s Exact test.

*p = .016 compared with corresponding vehicle group by Fisher’s Exact test.

Fig. 4. Survival rates of UK-68,798 and vehicle-treated animals subsequent to the development of posterolateral ischemia after left circumflex coronary intimal injury. At 1 h after the development of posterolateral ischemia in the presence of an anterior myocardial infarct, UK-68,798 significantly increased survival compared to vehicle treated control animals.

The mechanism for the antifibrillatory action of UK-68,798 in conscious animals is not known. Anterior wall infarct size, time to development of posterolateral ischemia and thrombus mass were not different between UK-68,798- and vehicle-treated groups. Furthermore, the drug did not affect the development of thrombus formation in the circumflex coronary artery in response to intimal wall injury and the subsequent development of ischemia remote from the infarct-related vessel. The observation that UK-68,798 prolonged the QTc interval and increased the ventricular ERP in the postinfarcted canine myocardium is in accord with electrophysiologic changes induced by other class III antiarrhythmic drugs such as CK-3579 and sematilide (Chi et al., 1990), E4031 (Lynch et al., 1990), d,l-sotalol (Lynch et al., 1984) and amiodarone (Patterson et al., 1983). The magnitude of the UK-68,798-mediated change in ventricular ERP is in the same range as that reported for other class III drugs (Chi et al., 1990; Lynch et al., 1990, 1984; Patterson et al., 1983). In the current study, UK-68,798 increased the ventricular ERP by a mean of 27 msec. The ventricular ERP was increased by 19, 30 and 24 msec by CK-3579, sematilide and E4031 (Chi et al., 1990; Lynch et al., 1990). In an unconscious canine preparation with a previous myocardial infarction, UK-68,798 increased the ventricular ERP by 24 msec and 20 msec (when paced at cycle lengths of 300 and 250 msec, respectively) (Zuanetti and Corr, 1991). The effect of UK-68,798 on the QTc interval in the current studies is in agreement with the results of Zuanetti and Corr (1991), as these authors also show an increased QTc interval after UK-68,798 treatment. As noted previously, the antifibrillatory action of these drugs may derive from their ability to counteract outward K+ current and the associated changes in the electrophysiologic properties of the ischemic heart. It may be relevant to the currently observed antifibrillatory effect that, in unconscious animals, UK-68,798 has been shown to reduce the dispersion of depolarization caused by rapid pacing (Gwilt et al., 1990).

The abbreviated action potential duration and enhanced potassium efflux contribute to the development of reentrant circuits within the ischemic myocardium, which represent the electrophysiologic mechanism most likely responsible for the development of serious ventricular arrhythmias (El-Sherif et al., 1981; Wit et al., 1982; Kramer et al., 1985). The increased potassium conductance during ischemia may involve ATP-dependent K+ channels in the heart (Noma, 1983). These channels are closed under normoxic conditions, but are opened during ischemia, when cellular ATP concentrations are reduced (Weiss and Lamp, 1989). The observation that glibenclamide, an ATP-dependent K+ channel blocker (Fosset et al., 1988), can reduce both myocardial potassium loss and the incidence of arrhythmias during ischemia (Kantor et al., 1990), provides evidence for the involvement of the ATP-dependent K+ channel in ischemia-induced arrhythmogenesis. However, because the ionic current responsible for the induction of fatal ventricular arrhythmias is unknown, and because the infarcted tissue is pathologically heterogeneous, regional specific variations in the “substrate,” which triggers the ventricular arrhythmia, may exist. The recent observation that rat ventricular muscle ATP-insensitive K+ channels are activated by arachidonic acid (Kim and Duff, 1990), which accumulates in ischemic myocardium as a result of membrane phospholipid degradation (Chien et al., 1984), indicates another possible mechanism for ischemia-effects were exerted in a dynamic situation of evolving myocardial ischemia and/or posterior infarction.
induced potassium loss. The role, if any, of the ATP-insensitive potassium channel in arrhythmogenesis is not known, however, but its activation by arachidonic acid further demonstrates that several factors may ultimately contribute to the genesis of ventricular arrhythmias and/or fibrillation. The role of what is putatively a K* channel controlling the time-dependent K* current, affected by UK-68,798 (Gwilt et al., 1991) in the pathogenesis of ventricular fibrillation, remains to be defined.

The dose of UK-68,798 used in this study (0.9 mg/kg) is higher than doses used in previously described studies (0.05 mg/kg; Zuanetti and Corr 1991). Preliminary studies in our laboratory did not demonstrate protection against sudden death (ventricular fibrillation) at doses of 0.10 mg/kg or 0.50 mg/kg of UK-68,798. It remains to be determined whether a significant antifibrillatory effect of UK-68,798 can be demonstrated at a dose less than 0.9 mg/kg. It is of interest that Zuanetti and Corr (1991) did not demonstrate antifibrillatory activity at a dose of 0.03 mg/kg. The effective dose of UK-68,798 required to suppress programmed electrical stimulation-induced ventricular arrhythmias and that required to prevent ischemia-induced ventricular fibrillation, therefore, may be different.

Despite a lack of understanding concerning the exact mechanism for the antifibrillatory action of UK-68,798 or related class III antiarrhythmic agents, there is now sufficient experimental data to suggest that this group of drugs possesses similar electrophysiologic properties and effects upon potassium conductance in ischemic myocardial tissue. The suggestion relating to the effect of these drugs on the ATP-dependent K* channel offers a challenging opportunity to exploit what may be an ideal approach to controlling disorders of heart rhythm and associated sudden cardiac death.

Acknowledgments

The authors thank Pfizer Central Research (Sandwich, U.K.) for the generous supply of UK-68,798 used in this study. The authors thank Dr. Roger A. Burgers from Pfizer Central Research for his constructive comments regarding the preparation of the manuscript.

References


Send reprint requests to: Benedict R. Lucchesi, Ph.D., M.D., Professor of Pharmacology, University of Michigan Medical School, M6322 Medical Science Building I, Ann Arbor, MI 48109-0626.