

UK-68,798, A Class III Antiarrhythmic Drug with Antifibrillatory Properties

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Sudden cardiac death is a significant cause of mortality in the United States, with an estimated 400,000 cases per year (11). Discovery of an effective antiarrhythmic drug capable of reducing the incidence of sudden cardiac death by as little as 10% would result in the saving of approximately 40,000 lives annually. Obviously, there is a need for an effective form of therapy capable of *safely* treating patients at risk of sudden cardiac death. The Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that antiarrhythmic therapy that successfully prevented asymptomatic and mildly symptomatic ventricular arrhythmias in post-myocardial infarction patients was associated with an increased risk of sudden cardiac death (32). Iatrogenic death is untenable and, therefore, an active search is underway for an antiarrhythmic drug that prevents (ideally), or reduces the probability of (at least), ventricular fibrillation or sudden cardiac death. Since certain currently available antiarrhythmic drugs (i.e., flecainide, encainide, and ethmozine) have proven to be inefficacious against sudden cardiac death (32), several antiarrhythmic drugs are currently under development. According to the Vaughan-Williams classification scheme, class III antiarrhythmic drugs increase the refractory period via an increase in the action potential duration, without altering the maximal rate of depolarization (33). Such an electrophysiologic mechanism may be ideal for the prevention of re-entrant arrhythmias, which constitute the predominant mechanism for life-threatening arrhythmias in humans (4). This review focuses on the recently developed class III drug, UK-68,798, a potent and efficacious antiarrhythmic agent with antifibrillatory properties. The review will discuss the chemistry, in vitro and in vivo cardiovascular pharmacology, mechanism of action, and pharmacokinetics of UK-68,798.

CHEMISTRY

The chemical name of UK-68,798 is 1-(4-methanesulfonamidophenoxy)-2-[N-(4-methanesulfonamidophenethyl)-N-methylamino]ethane. The structure of the drug is

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shown in Fig. 1. The molecular weight of the free base of UK-68,798 is 441.6 g/mol and the empirical formula is $C_{19}H_{27}N_3O_5S_2$ (7). For in vivo administration, UK-68,798 is freely soluble in dilute acid (HCl) media (acidified saline) (3,7). UK-68,798 is a weak acid (due to methanesulfonamido protons, with a pK_a of 9.0 and 9.6) and a moderate base (pK_a of 7.0), and at physiologic pH the sulfonamido groups are 2.45 and 0.63% ionized and the amine is 28.5% ionized (3). The melting point of the drug is 147–149°C (3). Structurally, the two methanesulfonamide functional groups at the terminal poles of the near-symmetric molecule are fundamentally important for the expression of class III antiarrhythmic activity (12). The methanesulfonamide functional group is a commonality among several relatively new compounds with demonstrated class III antiarrhythmic activity. Drugs with class III antiarrhythmic activity that possess the methanesulfonamide functional group include E-4031, sematilide, CK-3579, and *d*-sotalol (5,18).

PHARMACOLOGY

The cardiovascular pharmacology of UK-68,798 has been studied using both in vitro and in vivo experimental and clinical paradigms. These studies have defined the electrophysiologic effects of UK-68,798, which classify it as a class III antiarrhythmic drug according to the Vaughan-Williams classification scheme (33).

In Vitro Studies

The in vitro pharmacology of UK-68,798 was investigated using a variety of cardiac tissue and cell preparations, including myocardial trabeculae, papillary muscle, isolated Purkinje fibers, and isolated ventricular myocytes. Of the numerous electrophysiologic determinations made using in vitro preparations, an unequivocal finding is that the cardiac action potential duration is prolonged by UK-68,798. In guinea pig isolated papillary muscle, stimulated at a frequency of 1 Hz, and at concentrations of 10^{-8} through 10^{-6} M, UK-68,798 increased the action potential duration (APD) by 21–58% (31). Prolongation of the APD by UK-68,798 has been confirmed in canine isolated left ventricular trabecular muscle (12). In the canine preparation, UK-68,798 prolonged the APD at concentrations as low as 5 nM, and dose-dependently increased the APD to a maximal prolongation at 2 μ M. Both the APD_{50} (APD at 50% repolarization) and APD_{90} (APD at 90% repolarization) were increased by UK-68,798. The electrophysiologic effects of UK-

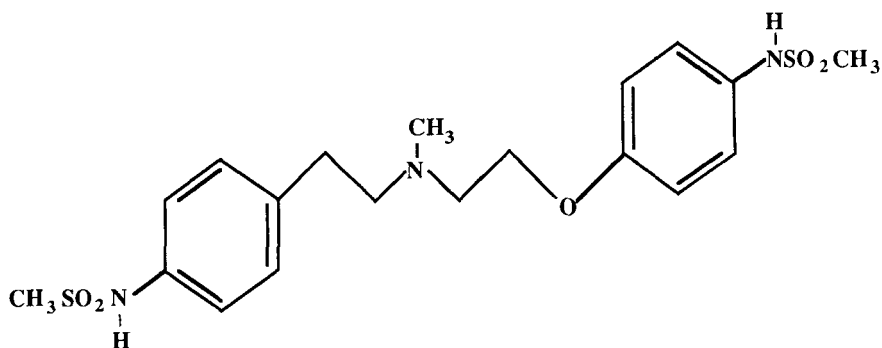


FIG. 1. Chemical structure of UK-68,798.

68,798 were selective, as the drug was without effect on the resting membrane potential, action potential amplitude, or the maximal rate of phase 0 depolarization (V_{max}) in the canine trabecular preparation; the drug had selective class III activity. UK-68,798 had similar electrophysiologic effects on the APD in isolated ventricular Purkinje fibers. Purkinje fibers were more sensitive to the effects of UK-68,798 than ventricular muscle. Concentrations as low as 1 nM prolonged the APD in Purkinje fibers, with maximal APD prolongation observed at 500 nM (12,17). The EC_{50} values for the effect of UK-68,798 on the APD₅₀ in cardiac ventricular tissue and Purkinje fibers were 30 ± 10 and 5.3 ± 1.4 nM, respectively, indicative of the greater sensitivity of the Purkinje fiber to the APD-prolonging effect of the drug (12). Others have confirmed the sensitivity of the Purkinje fiber to the APD-prolonging effect of UK-68,798, as the estimated EC_{50} for the APD₉₀ in an isolated canine Purkinje fiber preparation was 5.5 ± 0.9 nM (17).

The effective refractory period (ERP) of in vitro cardiac preparations was increased by UK-68,798. In guinea pig isolated papillary muscle stimulated at a frequency of either 1 or 5 Hz, UK-68,798 increased the ERP at concentrations of 5–1,000 nM (14). The increase in ERP was less at a stimulation rate of 5 Hz compared to 1 Hz. The conduction velocity was unaltered by UK-68,798 (12). The effect of UK-68,798 on the ERP of guinea pig isolated papillary muscle has been confirmed at concentrations of 10 nM to 1 μ M (31).

In addition to its electrophysiologic actions, UK-68,798 has negative chronotropic activity in vitro. In spontaneously beating guinea pig right atria, UK-68,798 dose-dependently reduced the rate of contraction (31,36). The negative chronotropic action of UK-68,798 in the atrial preparation was manifest at concentrations of 10^{-8} M and above (up to 10^{-5} M). The negative chronotropic effect of UK-68,798 was independent of β -adrenergic receptor blocking activity, as the dose–response curve to isoproterenol was not shifted to the left (the pD_2 value for the isoproterenol dose–response curve remained unaltered by UK-68,798) (36). However, the maximal chronotropic response to isoproterenol was attenuated by UK-68,798 to a value of $71 \pm 6\%$ of the maximum at a concentration of 10^{-5} M. The effect is indicative of noncompetitive inhibition. In contrast to the effect of UK-68,798, propranolol shifted the isoproterenol dose–response curve to the right (pD_2 value reduced), providing evidence that the atrial muscle paradigm discriminated β -adrenergic receptor antagonism.

Class III antiarrhythmic agents increase the APD without affecting the maximal rate of phase 0 depolarization (33). The cellular mechanism for class III antiarrhythmic activity may be an increase in inwardly directed currents (i.e., current flux through sodium channels), as with the sea anemone polypeptide ATX II (24), or inhibition of outwardly directed currents (i.e., current flux through potassium channels) as with amiodarone (1,29) and E-4031 (10). The electrophysiologic mechanism by which UK-68,798 exerts its class III effects is similar to other class III agents and related to the latter of these two possible mechanisms. There are a number of potassium channels with which the class III antiarrhythmic drugs may interact. Seven different potassium channels have been described in myocardial tissue and each may play a greater or lesser role in repolarization of the cell membrane. In guinea pig isolated ventricular myocytes, whole cell patch-clamp analysis has shown that UK-68,798 blocks a component of the delayed rectifier current (12). The delayed rectifier current is a function of two separate components, the “rapid” component (I_{kr}), which is time independent, and the “slow” component (I_{ks}),

which is time dependent (6,12). UK-68,798 blocks the "slow," time-dependent potassium current (I_{ks}) in guinea pig ventricular myocytes (12). The drug reduced the amplitude of the repolarizing I_{ks} at a concentration of 50 nM and effectively blocked the current at a concentration of 2 μ M. Therefore, the cellular mechanism by which UK-68,798 prolongs the APD and increases the ventricular refractory period is through antagonism of the "slow" component of the delayed rectifier current.

In Vivo Studies

The cardiovascular effects of UK-68,798 have been investigated using in vivo experimental paradigms. The canine species is the most frequently studied to date. In accord with results of in vitro studies, UK-68,798 exhibits class III antiarrhythmic activity in both conscious and unconscious in vivo preparations (3,8,14,37). The drug has been studied to a limited extent in humans.

The in vivo effect of UK-68,798 on electrocardiographic intervals provides evidence of its class III antiarrhythmic activity. In conscious and unconscious canines with a previous, surgically induced, anterior myocardial infarction, UK-68,798 prolonged the QT_c interval (2) [Bazett's corrected QT interval = QT interval in s/(R-R interval in ms)^{1/2}] and increased the ventricular ERP (3,8,14,37). As the QT_c interval approximates the ventricular APD, these data support the in vitro studies of APD prolongation by UK-68,798. A summary of the electrocardiographic effects of UK-68,798 from in vivo experimental studies is shown in Table 1. In conscious animals, UK-68,798 increased the ventricular ERP by a mean value of 27 ms (3). In the conscious canine preparation, the relative refractory period determined in the region of the anterior myocardial infarct was increased by UK-68,798 administration (169 ± 6 ms predrug vs. 186 ± 7 ms postdrug), and the ERP of the normal, noninfarcted myocardium also was increased (154 ± 12 ms predrug vs. 170 ± 11 ms postdrug) (3). Similarly, in an unconscious canine preparation, UK-68,798 increased the ERP with electrical stimulation from the normal, noninfarcted myocardium by mean values of 24 and 20 ms (when paced at cycle lengths of 300 and 250 ms, respectively) (37). With electrical stimulation from the peri-infarct region, UK-68,798 increased the ERP by a mean value of 23 ms (heart paced at cycle lengths of 300 and 250 ms) (37). The in vivo effects of UK-68,798 on the ventricular ERP in the unconscious canine was associated with lengthening of the ERP in the epicardial region surrounding the infarcted myocardium (37). The magnitude of UK-68,798-mediated alterations of the ventricular ERP was similar to those reported for other class III drugs (5,18,19,21). The ventricular ERP was increased by 19, 30, and 24 ms by CK-3579, sematilide, and E-4031, respectively (5,18). Therefore, the electrocardiographic effects of UK-68,798 are in accord with changes induced by other class III antiarrhythmic drugs such as CK 3579 and sematilide (5), E-4031 (18), *d,l*-sotalol (19), and amiodarone (21).

In conscious canines, UK-68,798 did not affect electrocardiographic intervals indicative of intracardiac conduction. The P-R interval and QRS duration were not influenced by UK-68,798 administration (3). The drug did not influence activation delay or conduction times determined in discrete, localized regions of normal, noninfarcted myocardium and infarcted myocardium (3). The lack of an effect of UK-68,798 on electrocardiographic indices of intracardiac conduction velocity has been confirmed by others both in conscious and anesthetized dogs, as P-Q, Q-R, and QRS intervals were unaffected by the drug (8,37).

TABLE 1. *In vivo* electrocardiographic and electrophysiologic effects of UK-68,798

Heat rate (beats/min)	ERP		QT _c		QT _p		P-R		QRS		Reference	
	UK	Control	UK	Control	UK	Control	UK	Control	UK	Control		
159 ± 19	143 ± 14*	ND	ND	350 ± 40	400 ± 30*	ND	ND	ND	ND	53 ± 8	53 ± 7	37
124 ± 7	118 ± 5	158 ± 7	184 ± 7*	299 ± 7	337 ± 8*	207 ± 5	221 ± 9*	99 ± 4	104 ± 4	60 ± 2	62 ± 2	3

ERP, effective refractory period (mV); QT_c, Bazett's corrected QT interval = QT interval in s/(R-R interval in ms)^{1/2}; QT_p, paced QT interval; P-R, P-R interval (ms); QRS, QRS complex duration (ms); ND, not determined.

* Significantly different from control.

Although a significant number of patients succumb to sudden cardiac death annually, determination of patients at risk remains somewhat problematic. For certain forms of heart disease, programmed electrical stimulation (PES) testing is a reliable method of identifying at-risk patients. In patients with a previous myocardial infarction, PES-induced ventricular tachycardia is the single best predictor of spontaneous ventricular tachycardia and sudden death (26). The ability of a drug to suppress PES-induced arrhythmias has been suggested as being indicative of a better prognosis for therapeutic success (25); however, others have provided evidence to the contrary (16). The prognostic value of PES testing is dependent upon several factors including the presence or absence of underlying cardiac disease, the form of the underlying disease (coronary artery disease, idiopathic cardiomyopathy, or ischemic heart disease), the type of induced tachycardia (sustained or nonsustained), and the presence of spontaneous ventricular arrhythmias, among other factors. PES testing is used clinically to determine patient response to antiarrhythmic drug therapy. PES testing may not predict uniformly the long-term clinical response to a given antiarrhythmic drug, as evidenced by the data in the CAST report (32). PES testing failed to predict long-term antifibrillatory efficacy. Despite this limitation, PES testing remains an applicable method of characterizing the putative antiarrhythmic efficacy of a drug. This should not be construed as being synonymous with antifibrillatory activity.

The antiarrhythmic efficacy of UK-68,798 has been studied in both unconscious and conscious canine preparations. In pentobarbital-anesthetized open chest dogs, PES-induced a sustained ventricular tachycardia 5 to 8 days after anterior wall myocardial infarction. The induction of the arrhythmia by PES was prevented by UK-68,798 (30 $\mu\text{g}/\text{kg}$) (37). The cycle length of the induced tachycardia, in the animals that remained inducible after UK-68,798 administration, was increased from 166 to 222 ms (37). In a conscious canine preparation with a previous anterior wall myocardial infarction, UK-68,798 (900 $\mu\text{g}/\text{kg}$) reduced the incidence of PES-induced ventricular arrhythmias by 50%, an incidence significantly lower than predrug inducibility (3). In the animals that remained inducible after UK-68,798 administration, the cycle length of the induced tachyarrhythmia was increased from 171 ± 23 to 201 ± 19 ms (3). Other class III drugs, such as sotalolol, E-4031, *d,l*-sotalolol, and bretylium, have protected against PES-induced ventricular tachycardia by 58 to 100% (18,19,22).

UK-68,798 possesses antiarrhythmic effects as determined by prevention of PES-induced ventricular tachyarrhythmias. The antifibrillatory properties of UK-68,798 have been studied using conscious and unconscious *in vivo* preparations. UK-68,798 was effective in significantly reducing the incidence of ventricular fibrillation in a conscious canine model of sudden coronary death (Fig. 2) (3). The model is one in which a previous anterior wall myocardial infarction results in a predictive, direct relationship between baseline inducible ventricular tachyarrhythmias and susceptibility to the development of lethal arrhythmias in response to a superimposed ischemic event in a region remote from the infarct-related artery (23,35). Sudden cardiac death, in the experimental model, was defined as death due to ventricular fibrillation within 1 h from the onset of posterolateral ischemia. Electrocardiographic evidence of regional ischemia (onset of ischemia) was manifested by ST-segment change and often associated with the appearance of coupled ventricular ectopic complexes. In the sudden death model, 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 in the absence of an effective

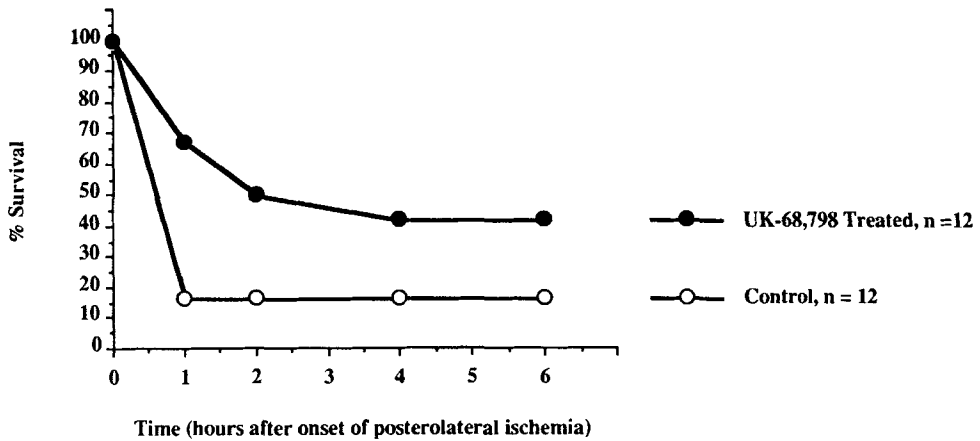


FIG. 2. Survival rates of UK-68,798- and saline vehicle-treated animals subsequent to the development of posterolateral ischemia following left circumflex intimal injury. At 1 h after the development of posterolateral ischemia in the presence of an anterior myocardial infarct, UK-68,798 increased survival compared to saline vehicle-treated control animals. Data from ref. 3.

antifibrillatory drug (see "control" data of Fig. 2) (23,35). Therefore, the critical time period (when ventricular fibrillation is most probable) is the first 60 min after the onset of ischemia, as opposed to a later time point when delayed death due to "pump failure" is the most likely cause of death. As shown in Fig. 2, the survival from sudden death was 17% in control vehicle-treated animals, while in the UK-68,798 treated animals, survival was 67%. The antifibrillatory effect of UK-68,798 in the conscious canine model of sudden cardiac death is in accord with results obtained with other class III antiarrhythmic drugs such as CK3579, sematilide (5), E-4031 (20), *d,l*-sotalolol (19), and amiodarone (21), in which the incidence of ventricular fibrillation, or sudden cardiac death, was reduced significantly when compared to a vehicle-treated control group. A beneficial effect of UK-68,798 against ventricular fibrillation is not unequivocal, however, as others have failed to demonstrate an antifibrillatory effect of UK-68,798. In an unconscious open chest canine model with a previous myocardial infarction, UK-68,798 did not protect against the incidence of ventricular fibrillation in response to PES testing (37). The latter study differed from that which showed a protective effect in two respects: (i) ventricular fibrillation was induced by PES testing, not ischemia (a putatively re-entrant mechanism), and (ii) the effective antifibrillatory dose of UK-68,798 [900 $\mu\text{g}/\text{kg}$ (3)] was higher than the doses used in the anesthetized dog studies (30 $\mu\text{g}/\text{kg}$) (37). Preliminary studies with the conscious canine model, however, did not demonstrate protection against sudden death (ventricular fibrillation) at doses of 0.10 or 0.50 mg/kg of UK-68,798 (L. Chi, personal communication). It remains to be determined whether significant antifibrillatory effects of UK-68,798 can be demonstrated at a dose less than 900 $\mu\text{g}/\text{kg}$, in the dosage range where antiarrhythmic efficacy has been demonstrated. The dose of UK-68,798 effective against ventricular fibrillation may be greater than that required to attenuate the development of PES-induced ventricular tachyarrhythmias. A salutary action of UK-68,798 against ventricular fibrillation is supported by data demonstrating that the drug reduced the dispersion of depolarization caused by rapid pacing (13), an effect that may contribute to the antifibrillatory properties of the drug. In view of the results of CAST, the

reduction in sudden cardiac death due to ventricular fibrillation associated with UK-68,798 treatment in the conscious canine model may be a highly relevant end point in the preclinical evaluation of this drug rather than its ability to prevent PES-induced ventricular tachyarrhythmias.

The precise electrophysiologic or pharmacologic mechanism for the antifibrillatory action of UK-68,798 in conscious animals has not been determined. However, a reduction in the dispersion of depolarization, possibly through prolongation of the APD or ERP, likely contributes in this regard. In conscious animal studies, in which the antifibrillatory effect of UK-68,798 was manifested during the development of a second myocardial infarction (ischemia-induced ventricular fibrillation), UK-68,798 did not influence the posterolateral wall infarct size (i.e., the size of the infarct developing subsequent to the onset of posterolateral ischemia), the time to the onset of posterolateral ischemia, or thrombus mass (3). Thus, the antifibrillatory action was not mediated through some indirect pharmacologic effect of the drug upon the processes leading to myocardial ischemia and infarction.

It has been suggested that the APD-prolonging effect of class III antiarrhythmic drugs may be inherently proarrhythmic (15). This suggestion derived from the view that the APD-prolonging effect of class III agents such as sotalol (30) and N-acetylprocainamide (9) exhibit *reverse* use dependence. Reverse use dependence implies that the magnitude of APD prolongation by class III agents is greater at slower heart rates than at faster heart rates (15). Thus, drugs with class III effects that maximally prolong the QT interval during bradycardia, or after a long diastolic interval (i.e., after an ectopic ventricular depolarization), may be associated with the development of torsades de pointes arrhythmias (27). Additionally, the intrinsic antiarrhythmic efficacy of class III agents may be limited because prolongation of the APD is of a lesser degree at higher heart rates when tachycardias are likely to develop, and drug efficacy is of greater importance. Since the APD-prolonging effect of UK-68,798 has been shown to be rate dependent in an isolated canine Purkinje fiber preparation [the degree of APD prolongation increased with increasing cycle length (17)], the *in vivo* administration of UK-68,798 may be associated with the development of arrhythmias due to excessive QT prolongation. Studies in the anesthetized dog, however, revealed that UK-68,798 increased the ERP to a similar extent at pacing cycle lengths of 300 and 250 ms. The results indicate that the efficacy of the drug was preserved at the higher pacing rate. This *in vivo* effect remains to be confirmed. Experimental and clinical evidence regarding the efficacy of class III agents, in general, indicates that concern for the possible drug-induced torsades de pointes and the potentially inherent inefficacy of the class III agents at higher heart rates may not be warranted. For example, under experimental conditions in the postinfarcted canine heart, the class III agents amiodarone, sotalol (5), and E-4031 (18) decrease the incidence of PES-induced ventricular tachyarrhythmias. Similarly, UK-68,798 reduces the incidence of PES-induced ventricular tachyarrhythmias in the canine heart after surgical induction of an anterior myocardial infarction (3,37). Additionally, UK-68,798 reduced the cycle length of the induced tachycardia in dogs that remained inducible after drug administration [the cycle length of the induced tachycardia increased from 171 ± 23 ms before drug to 201 ± 19 ms after drug (3)]. These results to date suggest that UK-68,798 may be an effective class III antiarrhythmic drug. Large clinical trials in humans will determine whether the potential for drug-induced torsades de pointes will negatively affect the therapeutic usefulness.

ness of UK-68,798, and whether the risk of this arrhythmia will be offset by antiarrhythmic and/or antifibrillatory efficacy of UK-68,798.

The effects of UK-68,798 on the *in vivo* heart rate are somewhat variable as increases and decreases in the intrinsic heart rate after drug administration have been reported. When studied in anesthetized dogs, UK-68,798, at doses in the 5–100 $\mu\text{g}/\text{kg}$ range, decreased the heart rate by 36 ± 6 beats/min from a baseline of 148 ± 8 beats/min at 100 $\mu\text{g}/\text{kg}$ only (14). At a dose of 30 $\mu\text{g}/\text{kg}$, UK-68,798 reduced the heart rate in an unconscious canine preparation (159 ± 19 beats/min predrug vs. 143 ± 14 beats/min postdrug, mean \pm SEM) (37). The influence of UK-68,798 upon the heart rate may depend on the central nervous system status of the animal, since in conscious dogs the heart rate changed to a lesser degree. At a dose of 100 $\mu\text{g}/\text{kg}$, the drug maximally reduced the heart rate by only 12 beats/min (8), and at a dose of 900 $\mu\text{g}/\text{kg}$, UK-68,798 did not change the heart rate (3). In human patients, the drug did not affect the heart rate at doses of 1.5, 3.0, and 4.5 $\mu\text{g}/\text{kg}$ (28).

Data on the effects of UK-68,798 in humans are limited. In patients with coronary artery disease, UK-68,798 at intravenous doses of 1.5, 3.0, and 4.5 $\mu\text{g}/\text{kg}$ increased the QT_c interval by 41, 40, and 81 ms and the uncorrected QT interval by 36, 52, and 83 ms, respectively (28). UK-68,798 did not affect the heart rate, blood pressure, PR interval, or QRS complex duration in the clinical population studied (28). The drug was reported to be well tolerated with no significant adverse effects (28). These preliminary data suggest that UK-68,798 exhibits class III antiarrhythmic activity in humans and is without potentially limiting adverse drug effects. The results of a chronic dosing schedule will provide important information regarding the longer-term consequences of exposure to the drug.

ADVERSE EFFECTS

In view of the results from CAST, the adverse effect profile of potential antiarrhythmic and/or antifibrillatory drugs is of considerable importance. In this regard, adverse effects attributable to UK-68,798 are limited due to the lack of available data. As indicated above, preliminary data suggest a favorable profile for the drug (28). Experimentally, studies of the antiarrhythmic properties of UK-68,798 have indicated that the drug may have proarrhythmic effects. In an *in vitro* study on the guinea pig isolated papillary muscle, early afterdepolarizations were observed in 2/11 (18%) preparations (31). In a conscious canine preparation, administration of UK-68,798 at a dose of 900 $\mu\text{g}/\text{kg}$ was associated with the appearance of spontaneous, transient ectopic ventricular complexes in 58% of the treated animals (3). These arrhythmias did not precipitate more serious rhythm disturbances (sustained or nonsustained ventricular tachycardia, or ventricular fibrillation), and dissipated 60 min after drug administration. Although limited in scope, these adverse effects (proarrhythmic) indicate that the drug has the potential to exacerbate or induce ventricular arrhythmias. It remains to be determined whether such arrhythmias will be manifest under clinical circumstances in patients receiving the drug.

PHARMACOKINETICS

The pharmacokinetic profile of UK-68,798 has been determined in dogs, normal human volunteers, and patients with coronary artery disease. In the dog, the terminal

elimination half-life of UK-68,798 was 4–6 h ($0.25\text{--}0.167\text{ h}^{-1}$), the volume of distribution was 4.0 L, and the clearance rate was 1.2 ml/min/kg (7). The oral bioavailability of UK-68,98 in the dog was determined to be between 72 and 100% (7). In human volunteers, after a 10 $\mu\text{g/kg}$ intravenous dose of UK-68,798, plasma levels of the drug declined in a biexponential manner with a termination half-life of 0.075 h^{-1} (34). After a 10 $\mu\text{g/kg}$ oral dose of UK-68,798, the peak plasma concentration was 2.5 ng/ml at 3 h after receiving the drug, and the terminal elimination half-life was 0.081 h^{-1} (34). Forty-eight hours after an intravenous or oral dose of UK-68,798 (10 $\mu\text{g/kg}$), the plasma concentration was 0.05–0.12 ng/ml (34). In patients with coronary artery disease, UK-68,798 exhibited first-order kinetics with a mean clearance rate of $4.7 \pm 1.2\text{ ml/min/kg}$, and a terminal elimination half-life of 9.7 h (0.103 h^{-1}) (28).

SUMMARY

This review examined the currently available but limited data regarding the antiarrhythmic and antifibrillatory actions of UK-68,798. The drug is a potent and efficacious class III antiarrhythmic agent capable of prolonging APD and ERP in ventricular muscle and Purkinje fibers without altering the maximum upstroke velocity of the membrane action potential. The data suggest that UK-68,798 produces minimal effects on the ventricular conduction time, while prolonging the APD and increasing ventricular refractoriness. The electrophysiologic basis for the APD prolongation of UK-68,798 relates to inhibition of the time-independent, delayed rectifier current. Although the mechanism of the antifibrillatory action of UK-68,798 and other related class III antiarrhythmic agents may not be defined precisely, there are sufficient experimental data to suggest that this group of drugs possesses similar electrophysiologic properties and has similar effects on potassium conductance in ischemic myocardial tissue, suggesting that potassium channel antagonism is important.

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