Depression of maximum rate of depolarization of guinea-pig ventricular action potentials by metabolites of encainide

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1 Standard microelectrode methods have been used to record action potentials from guinea-pig ventricular myocardium and dog Purkinje fibres, and to study the effects of the two major metabolites of encainide, O-desmethyl encainide (ODE) and 3-methoxy-O-desmethyl encainide (MODE).

2 In concentrations similar to those found in patients during chronic encainide therapy, neither ODE nor MODE produced significant depression of maximum rate of depolarization ($\dot{V}_{max}$) of action potentials in unstimulated tissue. Repetitive stimulation, however, was associated with depression of $\dot{V}_{max}$ which increased with increasing driving rates (rate-dependent block, RDB). At the fastest rate studied (interstimulus interval = 300 ms) ODE 1 μM depressed $\dot{V}_{max}$ by $47.5 \pm 5.7\%$ and MODE 1 μM , reduced $\dot{V}_{max}$ by $52.2 \pm 12\%$.

3 The onset and offset kinetics of this rate-dependent block were very slow. Full development of RDB during a train required over 100 action potentials and the time constants of recovery of $\dot{V}_{max}$ from RDB were 86.4 ± 37 s for ODE and 100.4 ± 18 s for MODE. The amount of RDB and its rate of onset increased with drug concentration. The recovery time constants were independent of interstimulus interval or drug concentration. Both metabolites also produced rate-dependent depression of conduction velocity in canine Purkinje fibres, but no evidence of selective depression of conduction of interpolated premature potentials was seen.

4 Early afterdepolarizations occurred spontaneously in three preparations in the presence of MODE, 1 μM and one preparation in ODE, 1 μM .

5 It is concluded that these metabolites of encainide may play a role in producing both its antiarrhythmic and its proarrhythmic effects.

Introduction

Encainide is a new class 1 antiarrhythmic drug (Byrne *et al.*, 1977; Gibson *et al.*, 1978; Harrison *et al.*, 1980; Roden *et al.*, 1980). Recent trials have shown it to be at least as effective as disopyramide and quinidine in suppressing chronic ventricular arrhythmias (Caron *et al.*, 1985; Morganroth *et al.*, 1986). It is now known that some 90% of humans ('fast metabolizers'), rapidly transform encainide into

two main metabolites, O-desmethyl encainide (ODE), and 3-methoxy-O-desmethyl encainide (MODE). The other 10% produce very little or no ODE or MODE, but produce measurable amounts of third metabolite, N-desmethyl encainide (NDE). All of these metabolites possess potent class 1 antiarrhythmic actions of their own (Carey *et al.*, 1984; Davy *et al.*, 1986; Barbey *et al.*, 1988). Because they have longer elimination half-lives than encainide, MODE and ODE tend to accumulate in the plasma of patients on chronic oral therapy and reach concentrations well in excess of the parent compound

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(Kates *et al.*, 1982). Furthermore, it has been suggested that ODE in particular, may contribute significantly to the clinical effects of encainide (Carey *et al.*, 1984).

A number of recent studies have demonstrated that there are major differences between class 1 antiarrhythmic drugs in terms of their kinetics of interaction with the fast inward sodium channel, and these findings can explain a number of the clinically observed differences between the various subclasses, 1A, 1B and 1C, within this important group of compounds (Campbell, 1983a; Harrison, 1985). Encainide itself has been shown to have very slow kinetics (group 1C; Campbell, 1983b), so that at therapeutic concentrations, it tends to depress conduction of sinus beats and premature beats almost equally, thus prolonging intracardiac conduction times significantly (Pallandi & Campbell, 1988). MODE and ODE have been shown to produce rate-dependent depression of $\dot{V}_{max}$ (maximum rate of depolarization) of cardiac action potentials, as do all class 1 antiarrhythmic agents (Elharrar & Zipes, 1982), but these workers did not study the kinetics of onset and offset of these rate-dependent effects, nor their ability to depress $\dot{V}_{max}$ in the absence of prior stimulation ('resting block'). The present study was carried out to characterize the two major metabolites of encainide in terms of these parameters, at concentrations similar to those found in patients on chronic therapy with the parent drug.

Methods

Guinea-pig experiments

Guinea-pigs of either sex weighing 500–800 g were decapitated and their hearts quickly removed. Strips (approximately 5 mm × 3 mm × 1 mm) were cut from the right ventricular free wall and pinned to the base of a bath (volume 0.5 ml). The tissue was superfused at 3 ml min⁻¹ with modified Locke solution gassed with 95% O₂ and 5% CO₂ and maintained at 37°C ± 0.2°C by a Peltier element. The composition of the Locke solution was as follows (mM): NaCl 125, KCl 5.6, CaCl₂ 2.16, NaHCO₃ 25, MgCl₂ 1.0, NaH₂PO₄ 0.44, glucose 11 and the pH was 7.4. Preparations were allowed to equilibrate for 1 h before taking recordings. During this time and throughout the experiment, they were driven from bipolar platinum electrodes providing rectangular pulses of sufficient amplitude to limit variations in latency (between stimulus and action potential upstroke) to less than 1 ms (Walton & Fozzard,

1979). Action potentials were recorded from cells on the surface of the preparations by use of conventional glass microelectrodes filled with 3 M KCl, coupled to a high input impedance d.c. amplifier with negative capacitance compensation (Neurolog). To study rate-dependent effects the preparations were driven at interstimulus intervals (ISI) varying from 300–4800 ms. Trains of stimuli were of sufficient duration to achieve a stable level of effect and rest periods (unstimulated) of at least 5 min were interposed between trains to allow full recovery from rate-dependent effects. The time course of this recovery process was studied by adding a single extra-stimulus at varying intervals after a series of identical trains of stimuli at constant ISI (Campbell, 1982). The effective refractory period (ERP) was measured by interpolating single premature stimuli (S2), after every tenth basic drive stimulus (S1) at a constant interstimulus interval of 1000 ms. The S1-S2 interval was progressively decreased until no propagated action potential resulted from the S2.

Action potentials were monitored on an oscilloscope and sampled at 27 kHz using a DT 2801-A Analog-digital converter fitted to an IBM-PC. Analysis was performed by software developed within the Department (the absolute value of the maximum rate of depolarization being calculated by simple differencing of adjacent samples).

Dog experiments

The preparation has been described elsewhere (Pallandi & Campbell, 1988). Cardiac Purkinje fibres (8–15 mm long and 0.5–1.5 mm in diameter) were obtained from a total of 6 adult mongrel dogs anaesthetized with sodium pentobarbitone. The fibres were rapidly removed and mounted in the base of a tissue bath (volume 0.5 ml) and superfused at 3 ml min⁻¹ with modified Locke solution gassed with 95% O₂ and 5% CO₂. They were driven from one end by stimuli from a Grass S11 Stimulator, delivered through a bipolar platinum electrode. The stimuli were rectangular pulses 4 ms long and of sufficient amplitude to maintain a constant latency between the stimulus and the upstroke of the action potential recorded at the proximal microelectrode. Two microelectrodes (5–12 mm apart) were used to record intracellular action potentials. These are referred to as proximal and distal, relative to the position of the extracellular stimulating electrode. They were coupled to a dual high input-impedance d.c. amplifier (WPI 750). Action potentials were monitored on an oscilloscope screen and analysed by digital techniques using a Rockwell AIM-65 8-bit microcomputer modified by the addition of a gain-matching amplifier, a sample-and-hold circuit and an

Analog Devices ADC 571 10-bit analog-to-digital converter. The analysis was as previously described (Campbell, 1987), with the addition of software capable of measuring the time between action potential upstrokes recorded in the proximal and then the distal microelectrode. This was converted into an estimate of conduction velocity by dividing the conduction time into the measured distance between the microelectrodes. The composition of the superfusate (kept at $37 \pm 0.5^\circ\text{C}$ by a Peltier element) was the same as for the guinea-pig experiments.

The samples of MODE and ODE were kindly provided by Bristol-Myers, Australia. All data are given as means $\pm$ s.d. and significance of differences between means estimated by Student's *t* test or the paired *t* test, as appropriate.

Results

Guinea-pig experiments

No obvious effects on action potential duration (APD) were noted for ODE or MODE but the experimental protocol involved frequent changes of stimulation rate and made accurate assessment of drug actions on this parameter impossible.

Class 1 effects, (reduction of maximum rate of depolarization), were evident within 5 min, and maximal within 15–20 min. They reversed completely with one hour of washing.

Resting block The ability of ODE and MODE $1 \mu\text{M}$ to depress $\dot{V}_{\max}$ in the absence of prior stimulation, was studied by impaling single ventricular myocytes in control solution, and then superfusing with cumulative concentrations of drug. Single action potentials were stimulated after 60 min exposure time and their $\dot{V}_{\max}$ measured and compared to the control value. Neither ODE ($n = 8$), nor MODE ($n = 6$) produced any statistically significant resting block.

Rate-dependent depression of $\dot{V}_{\max}$ In contrast to the lack of resting block, repetitive stimulation produced large declines in $\dot{V}_{\max}$ which slowly approached a new plateau value after 1–2 min of stimulation at a given interstimulus interval (ISI). The extent of this 'rate-dependent block' increased monotonically as the ISI was shortened from 4800 ms to 300 ms. It also increased with concentration (Figure 1). At the fastest stimulation rates (ISI = 300 ms), $1 \mu\text{M}$ ODE depressed $\dot{V}_{\max}$ $47.5 \pm 5.7\%$ from control ($n = 10$ cells; $P < 0.0001$),

Figure 1 Relationships between stimulation rate (expressed as interstimulus interval) and the percentage rate-dependent reduction of $\dot{V}_{\max}$ at two concentrations of O-desmethyl encainide (ODE, a) and 3-methoxy-O-desmethyl encainide (MODE, b). (●) Control; effect of ODE (a) or MODE (b) (■) $1 \mu\text{M}$ and (▲) $0.25 \mu\text{M}$. Each point represents the mean and vertical lines show s.e.mean.

and the corresponding value for $1 \mu\text{M}$ MODE was $52.2 \pm 12.0\%$ ($n = 6$; $P < 0.0001$). The actual baseline values (at ISI = 4800 ms) for $\dot{V}_{\max}$ in control solution were $250 \pm 25 \text{ V s}^{-1}$ for the 10 cells later exposed to ODE and $286 \pm 35 \text{ V s}^{-1}$ for the six cells exposed to MODE.

Kinetics of onset of rate-dependent block The kinetics of onset of rate-dependent depression of $\dot{V}_{\max}$ during a train of stimuli following a long rest period (5 min) were very slow, with equilibrium only occurring after 1–2 min of stimulation. The decline in $\dot{V}_{\max}$ between the first and second beats of a train was always less than 5% of the final reduction achieved at equilibrium. Estimates were made of the rate at which $\dot{V}_{\max}$ fell to its equilibrium value during stimulation at ISI = 300 ms. This process was fitted to a simple exponential and onset rate expressed in

Table 1 Conduction velocity (m s^{-1}) at stated interstimulus intervals

	1000	800	Interstimulus interval (ms)		400	300
			600	500		
Control ($n = 6$)	2.04 ± 0.36	1.94 ± 0.33	1.91 ± 0.35	1.91 ± 0.33	1.91 ± 0.33	1.91 ± 0.33
ODE $1 \mu\text{M}$ ($n = 6$)	1.74 ± 0.66	$1.63 \pm 0.61^*$	$1.51 \pm 0.58^{**}$	$1.41 \pm 0.51^{**}$	$1.38 \pm 0.58^{**}$	$1.27 \pm 0.58^{**}$
MODE $1 \mu\text{M}$ ($n = 6$)	$1.42 \pm 0.34^{**}$	$1.40 \pm 0.34^{**}$	$1.29 \pm 0.35^{**}$	$1.19 \pm 0.39^\dagger$	$1.12 \pm 0.38^\dagger$	$1.03 \pm 0.37^\dagger$

Data shown are means $\pm$ s.e.mean. ODE = O-desmethyl encainide and MODE = 3-methoxy-O-desmethyl encainide.

* $P < 0.05$; ** $P < 0.01$; $^\dagger P < 0.001$; significance of difference from controls.

terms of the slope of that exponential (Courtney, 1979). The value obtained for $1 \mu\text{M}$ MODE was $0.011 \pm 0.003 \text{ AP}^{-1}$ (AP = action potential), and for $1 \mu\text{M}$ ODE $0.012 \pm 0.004 \text{ AP}^{-1}$. The difference between the metabolites was not significant.

Kinetics of recovery from rate-dependent block Recovery of $\dot{V}_{\max}$ towards its 'resting' level at the end of a train of stimuli followed an exponential time course that was independent of drug concentration or ISI. For ODE the time constant of recovery of $\dot{V}_{\max}$ (τ_{re}) was $86.4 \pm 37.4 \text{ s}$ ($n = 15$), and for MODE, $100.4 \pm 18.2 \text{ s}$ ($n = 10$; NS).

Effects on refractory period Neither drug was able to prolong the effective refractory period (ERP), relative to the action potential duration (measured to 97% repolarization; APD_{97}). In fact, if anything there was a trend in the opposite direction which did not achieve statistical significance, possibly due to the large variation seen between preparations. The control value for ERP- APD_{97} for cells subsequently exposed to ODE was $13.4 \pm 10.8 \text{ ms}$. ERP- APD_{97} in the presence of $1 \mu\text{M}$ ODE was $6.6 \pm 12.8 \text{ ms}$ ($n = 8$; NS). Corresponding figures for $1 \mu\text{M}$ MODE were $4 \pm 12 \text{ ms}$ (control) and $-7 \pm 11 \text{ ms}$ (MODE; $n = 8$; NS).

Dog experiments

Purkinje fibres from six dogs were used to test the hypothesis that the kinetics of the actions of ODE and MODE on $\dot{V}_{\max}$ in guinea-pig ventricle would correlate with the effects of these compounds on conduction velocity (at least in tissue which approximates reasonably well to a linear cable model).

Effects at steady-state In this series of experiments, the preparation was driven for at least 3 min at each

of a series of increasing rates (ISI = 1000, 800, 600, 500, 400 and 300 ms). This was done first in control solution and then after 20 min exposure to ODE or MODE, $1 \mu\text{M}$.

In the absence of drug, there was a small (non-significant) reduction in conduction velocity as stimulation rate increased (Table 1). Conduction velocity at ISI = 1000 ms was reduced in the presence of both drugs (only significant for MODE at this slowest rate) and these effects became greater as ISI was progressively shortened.

Rate of decline of conduction velocity after a reduction in interstimulus interval As was noted for $\dot{V}_{\max}$, both drugs achieved a new steady-state value for conduction velocity very slowly after a step increase in stimulation rate, requiring > 100 beats to do so.

The (much smaller) falls in conduction speed seen during similar trains in control solution were complete within 2–3 beats.

Effects on conduction of single premature beats The second way in which the effects of sudden changes in rate were studied involved the interpolation of progressively more premature extrastimuli (S2) following every tenth basic drive stimulus (S1), at ISI = 1000 ms. Because of possible drug-induced variations in action potential duration, the diastolic interval was considered a more useful measure of degree of prematurity than the S1-S2 interval. The diastolic interval is the period between the end of the last action potential in the normal drive cycle (defined at 97% repolarization), and the premature extrastimulus (S2).

In control solution, the conduction velocity of the premature action potential remained exactly the same as that of the basic drive action potentials except where diastolic interval approached zero (i.e. premature action potential arising during repolariza-

tion of preceding potential; Pallandi & Campbell, 1988). Essentially the same behaviour was observed in the presence of $1\ \mu\text{M}$ ODE and MODE. Values for conduction velocity were reduced in the presence of drug (as detailed in Table 1), but no significant reduction in the conduction velocity of the premature beat below that of the basic drive beat was seen at diastolic intervals above zero.

Early afterdepolarizations Interruption of repolarization, with transient repolarizations occurring during the plateau phase of action potentials, was observed as a chance finding at slow drive rates ($\text{ISI} \geq 1000\ \text{ms}$) on three occasions in the presence of $1\ \mu\text{M}$ MODE (2 out of 8 guinea-pig ventricle and 1 out of 6 dog Purkinje fibre preparations), and on one occasion out of 8 during superfusion of guinea-pig ventricular cells with $1\ \mu\text{M}$ ODE. In all cases full repolarization eventually occurred after 1–3 oscillatory cycles during the plateau, which led to extreme prolongation of the action potential. These early afterdepolarizations always disappeared quickly when the ISI was reduced to approximately 800–600 ms.

Discussion

The studies on guinea-pig ventricle confirm the findings of Elharrar & Zipes (1982), and provide in addition, much data on the kinetics of onset and offset of these actions. Elharrar & Zipes did not study the ability of ODE or MODE to reduce $\dot{V}_{max}$ in the absence of stimulation ('resting block' of the sodium channel). The ability to produce resting depression of $\dot{V}_{max}$ correlates well with lipophilicity for class 1 agents of relatively low molecular weight (Sada & Ban, 1981), but this relationship breaks down for drugs with molecular weights above about 350 (Campbell, 1983c; Courtney, 1987). Encainide which has a relatively high molecular weight (352) and is relatively lipid insoluble, shows a similar inability to produce resting block (Campbell, 1983b). It is not surprising therefore, that ODE and MODE which have similar molecular weights to encainide (337 and 396), and share its hydrophilicity, exhibit a similar lack of resting block.

The present study has confirmed the findings of Elharrar & Zipes (1982) that both ODE and MODE are significantly more potent than encainide at producing rate-dependent reduction of $\dot{V}_{max}$. In addition, the onset of this effect has been shown to be at least as slow as for encainide, requiring some 1–3 min stimulation or over one hundred beats to achieve equilibrium. Less than 5% of the final degree

of rate-dependent block achieved during stimulation at a given ISI occurred between the first and second beats of a train. Corresponding figures for drugs such as lignocaine and mexiletine which exhibit fast onset kinetics (1B agents) are of the order of 90% and 60% (Campbell, 1983a). The offset kinetics of the two metabolites were significantly slower than for the parent compound ($\tau_{re} = 86.4\ \text{s}$ for ODE and $100.4\ \text{s}$ for MODE compared to $20.3\ \text{s}$ for encainide in the same preparation; $P < 0.01$ in both cases; Campbell, 1983b).

It is not surprising therefore, that at concentrations comparable to those found in patients on chronic oral therapy with encainide (see below), neither ODE nor MODE had any significant effect on ERP relative to APD nor demonstrated any selective depression of conduction in premature extrasystoles. This last finding is consistent with the work of Dresel (1984), and confirms a correlation between kinetics of drug action and effects on conduction velocity as shown previously for other agents (Man & Dresel, 1979; Pallandi & Campbell, 1988).

Clinical relevance of concentrations studied

Kates *et al.* (1982) studied 13 patients on chronic encainide therapy and found mean plasma concentrations of encainide, ODE and MODE of respectively $56.3\ \text{ng ml}^{-1}$ (159 nm), $214.6\ \text{ng ml}^{-1}$ (500 nm) and $184.6\ \text{ng ml}^{-1}$ (547 nm). Barbey *et al.* (1988) actually administered ODE and MODE to 9 patients with ventricular arrhythmias and found minimal effective concentrations of approximately $160\ \text{nm}$ for ODE and $300\ \text{nm}$ for MODE. Thus the concentrations used in the present study ($250\ \text{nm}$ and $1\ \mu\text{M}$) are clinically meaningful and the effects observed are likely to be comparable to those seen in patients on long-term treatment with encainide.

Significance of early afterdepolarizations

There is a rapidly increasing awareness of the potential ability of many antiarrhythmic agents, particularly class 1 drugs, to increase the frequency and/or severity of clinical arrhythmias in a minority of patients (Podrid, 1985; Zipes, 1988). Recent evidence has implicated early afterdepolarizations (such as those observed with ODE and MODE in the present study) in the pathogenesis of some of these 'proarrhythmic' effects, particularly in the genesis of a bizarre form of ventricular tachycardia characteristic of drug-induced arrhythmias, known as 'torsade de pointes' (Roden & Hoffman, 1985). It is interesting in this context to note that the incidence of

proarrhythmic effects in a number of studies of this phenomenon, has been higher for patients on encainide than for any other agent (Winkle *et al.*, 1981; DiBianco *et al.*, 1982; Podrid, 1985; Morganroth *et al.*, 1986; Zipes, 1988). Incidences of arrhythmia aggravation of 12–25% or more have been found for this agent.

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It seems reasonable to speculate that one or both of these metabolites may play an important role not only in producing the antiarrhythmic effects of encainide, but in its proarrhythmic actions as well.

This work was supported by the National Health and Medical Research Council of Australia.

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(Received November 14, 1988

Revised January 26, 1989

Accepted February 13, 1989)