Suppression of Longitudinal Versus Transverse Conduction by Sodium Channel Block

Effects of Sodium Bolus

Jacques Turgeon, PhD; Todd A. Wisialowski, BSE; Wilson Wong, MD; William A. Altemeier, BSE; John P. Wikswo Jr., PhD; and Dan M. Roden, MD

Background. Arrhythmias resulting from treatment with sodium channel-blocking antiarrhythmic drugs have been successfully treated with sodium infusion, although the mechanism underlying this effect is uncertain.

Methods and Results. In this study, we used a multielectrode array to examine the effects of O-desmethyl encainide (ODE), a potent sodium channel-blocking metabolite of encainide, on conduction in canine ventricle. ODE depressed both longitudinal and transverse conduction velocities in a plasma concentration-related fashion (r = −0.74, −0.60; p < 0.001). At ODE concentrations ≤300 ng/ml (n = 34), conduction velocity was depressed to the same extent in the longitudinal (−21.9±8.4%, SD) and transverse orientations (−22.0±8.8%). However, at concentrations >300 ng/ml (n = 17), conduction was significantly more impaired longitudinally than transversely (−44.5±11.7% versus −34.4±13.7%, p < 0.02). In 12 animals with high concentrations (mean, 432±32 ng/ml), a 5-meq/kg bolus of sodium chloride over 1 minute immediately increased conduction velocity; this effect was significantly greater and longer lasting in the longitudinal orientation. In two animals, conduction block in the longitudinal orientation was documented at high plasma ODE and was immediately reversed by sodium bolus.

Conclusions. We conclude that the major effect of sodium in animals with excess sodium channel block is improvement of longitudinal propagation; this effect may underlie the antiarrhythmic action of sodium in the analogous clinical setting. (Circulation 1992;85:2221–2226)

KEY WORDS • sodium channel block • conduction • anisotropy

Block of cardiac sodium channels, a common mode of antiarrhythmic drug action, results in conduction slowing in the His–Purkinje system and ventricular muscle.1 Ventricular muscle is highly anisotropic; that is, its electrophysiological properties are strongly dependent on the orientation of and connections between long, thin myocytes.2-4 When cardiac muscle is stimulated by a point source, impulses propagate two to three times faster in the longitudinal than in the transverse orientation, creating ellipsoidal isochrones.4,5 Cells are ordinarily well coupled end-to-end; longitudinal propagation is thought to be more dependent on the magnitude of the sodium current than is transverse propagation, which is thought to depend on the geometrical arrangement and extent of cell–cell coupling in the transverse orientation as well as on sodium current.6 In experiments in which the effects of the sodium channel blockers on longitudinal and transverse propagation have been assessed, conduction is depressed in both orientations. In most studies, the extent of conduction slowing is greater in the longitudinal orientation, although the differences between drug effects in the two orientations are sometimes quite small.8–10

An agent that only slows conduction, particularly within a latent reentrant circuit, has the potential to enable rather than to suppress a reentrant tachycardia. The association between marked conduction slowing and ventricular tachycardia has long been recognized during treatment with sodium channel blockers. Indeed, the ventricular tachycardia associated with the class IC agents encainide and flecainide during the early 1980s11,12 was also seen during the mid-1950s when high doses of quinidine were often used, particularly in the conversion of atrial fibrillation.13 The administration of sodium as lactate, bicarbonate, or chloride can acutely reverse marked QRS prolongation seen as a consequence of sodium channel block, and this intervention can be antiarrhythmic.14–20 The effect of sodium has been documented not only with quinidine and procainamide and with class IC agents but also with antidepressant drugs, in which bicarbonate may be particularly important.21 The way in which sodium alters local conduction in this setting is not known.

We now report on the effects of a range of concentrations of O-desmethyl encainide (ODE), a potent sodium channel-blocking metabolite of encainide,22,23 on longitudinal and transverse propagation in ventricular muscle. As well, we have evaluated the effects of a
bolus of sodium on longitudinal and transverse propagation during ODE treatment to develop a further understanding of the mechanism of action of the sodium in this setting.

**Methods**

The methods are similar to those we have used in our previous studies of excitation in canine ventricle and are repeated here.

**Surgical Preparation**

Mongrel dogs of either sex were anesthetized with intravenous sodium pentobarbital (30 mg/kg), intubated, and ventilated with room air (Harvard respirator) supplemented by oxygen. A left lateral thoracotomy was performed in the fifth intercostal space, and a pericardial cradle was created. A Lucite ring for placement of the recording electrode described below was then sutured to the left ventricular epicardial lateral to the left anterior descending artery. The right femoral artery was cannulated to continuously monitor blood pressure and to obtain blood samples. Arterial blood gas samples were analyzed (Corning 158), and ventilator settings were adjusted to ensure normal arterial pH (7.35–7.45) and adequate oxygenation (PO2 > 80 mm Hg). The left femoral vein was cannulated to infuse ODE, and the right femoral vein or external jugular vein was cannulated for administration of sodium chloride boluses. Surface ECG leads I, II, and III were monitored continuously.

**Data Acquisition**

A planar electrode array with four pairs of closely spaced bipolar electrodes (interbipole distance of 1.5 mm) along two perpendicular axes was used to record direction-dependent propagation (Figure 1). The bipoles were made of 250-μm-diameter silver wire threaded through a thin Plexiglas disk, soldered to flexible insulated leads, and sealed with epoxy. A central titanium stimulating electrode was used as the cathode. A distant anode, a stainless-steel wire, was sewn onto the right ventricle. The electrode array was introduced into the Lucite ring and clamped in place by small setscrews. Stimuli (pulse width, 0.5 msec; two to four times threshold) were delivered at a cycle length (CL) of 300 msec, and the local electrograms from four bipoles along each of two perpendicular directions were monitored. The orientation of the array was adjusted by rotating the electrode within the sewing ring until the time difference between the signals recorded at bipoles 4 and 8 was maximized (Figure 1), thereby defining the direction of fastest (longitudinal) and slowest (transverse) epicardial propagation.

The signals from each of eight bipolar electrodes (four in the longitudinal and four in the transverse direction) were processed with high-gain amplifiers (×10) and bandpass-filtered between 0.01 Hz and 1 kHz. Ten processed signals were then collected by a stand-alone digital acquisition unit (TransEra Corp., MDAS 7000) at a sampling rate of at least 2 kHz and signal-averaged. The signals were output over an IEEE-488 standard parallel bus (Hewlett-Packard, HP1B) to a 16-bit microcomputer for storage. The MDAS 7000 and the computer were both controlled by software written in QUICKBASIC (Microsoft Corp.). Ventricular pacing was started at least 30 seconds before data acquisition. Animals were allowed to stabilize for a period of 30 minutes after the end of instrumentation before any further procedures were initiated.

**ODE Dosage Regimens**

ODE (obtained from Bristol-Myers, Wallingford, Conn.) was infused as a series of loading and maintenance infusions designed to achieve stable plasma ODE concentrations during the maintenance period, thereby allowing assessment of the effects of sodium on ODE-induced conduction slowing. The low-dose regimen was a loading dose administered as a priming infusion of 17 μg/kg/min for 1.5 minutes followed by a second infusion of 12 μg/kg/min for 13.5 minutes and a maintenance infusion of 6 μg/kg/min. To achieve higher concentrations, the initial regimen was used with a 30-minute maintenance infusion and followed by a second loading dose administered as a priming infusion of 22.8 μg/kg/min for 7.8 minutes followed by a second infusion of 17 μg/kg/min for 7.2 minutes and a maintenance infusion of 12 μg/kg/min. All drug infusions were administered with a Harvard compact infusion pump (model 975). Conduction velocity was recorded at baseline and at least 30 minutes after the start of the maintenance infusion. We have used this method of administering ODE to study a series of studies of modulators of impulse initiation and propagation. For this report, we include data on the effects of ODE on conduction gathered in 25 animals in these studies as well as in 14 animals studied for the purposes of this report during both the low dose and the higher dose of ODE. In these 14 animals, the effects of sodium boluses during high-maintenance ODE concentrations were studied and are also reported.

Samples for subsequent analysis of plasma ODE were obtained during the maintenance infusion before and during the interventions described below. As well, samples for measurement of serum Na+ and K+ were obtained during the study periods described below.

**Administration of NaCl**

Forty-five minutes after the beginning of the second maintenance infusion, a bolus of sodium chloride
(5 meq/kg; 5 M solution) was injected over 1 minute while ODE maintenance infusion was kept constant. A second bolus was injected 23 minutes later. Data (conduction velocity and plasma Na⁺ and K⁺ samples) were acquired at baseline and 30 and 45 minutes after the beginning of the second maintenance infusion of ODE, at 1, 5, 10, 15, and 20 minutes after the end of the first sodium chloride bolus, and at 1, 5, and 10 minutes after the end of the second bolus.

**Plasma Sample Analysis**

Plasma concentrations of ODE were determined by high-performance liquid chromatography. Sodium and potassium concentrations were analyzed by flame photometry (model 343, Laboratory Instrumentation, Lexington, Mass.).

**Data Analysis**

Data analysis was performed by a batch operation using software written in ASYST 2.0 (MacMillan Software). For each data set, a least-squares polynomial fitting routine was performed on each bipolar signal to determine the peak voltage, defining the arrival time of the propagating depolarizing wave front under the bipole. Linear regression of the bipolar distance from the central cathode versus arrival time was then used to determine longitudinal (θ_LONG) and transverse (θ_TRANS) conduction velocities.

Two-way ANOVA was performed to detect significant differences between multiple means. A probability value of less than 0.05 was sufficient to reject the null hypothesis. Pairwise analysis using Duncan’s multiple comparison procedure was performed on data sets for which significant differences were detected by ANOVA. All values are expressed as mean±1 SD.

**Results**

**Depression of θ_LONG Versus θ_TRANS**

Mean baseline epicardial conduction velocity was 0.54±0.02 m/sec in the longitudinal direction and 0.22±0.01 m/sec in the transverse direction. The relation between maintenance plasma ODE and conduction slowing in the longitudinal and transverse orientations is shown in Figure 2. Data from two animals with conduction block in the longitudinal orientation at high plasma ODE (484, 513 ng/ml) are not included in Figure 2 and are discussed further below. The left panel of Figure 2 shows that changes in θ_LONG and θ_TRANS were both significantly correlated with plasma ODE; however, the concentration dependence of the changes in θ_LONG was steeper than that for θ_TRANS. For the 14 animals studied exclusively for the purposes of studying the effects of sodium on local conduction, the extents of decrease in θ_LONG and θ_TRANS were similarly highly correlated with plasma ODE (r=-0.76 and -0.79, respectively, both p<0.001). Inspection of the left panel suggests that the greatest differences between longitudinal and transverse changes were at the higher concentrations. The right panel shows the same data grouped by ODE concentrations ≤300 ng/ml (two thirds, 34 of 51 of the data sets) and those >300 ng/ml (highest third, 17 of 51 of the data sets). The changes in θ_LONG and θ_TRANS were virtually identical at ≤300 ng/ml (−21.9±8.4% versus −22.0±8.8%, θ_LONG versus θ_TRANS) but significantly greater in the longitudinal orientation (−44.5±11.7% versus −34.4±13.7%, p<0.02) at concentrations >300 ng/ml.

**Effects of Sodium**

The effects of sodium chloride boluses in 12 animals with high ODE concentrations (432±32 ng/ml) are shown in Figure 3. Sodium chloride boluses transiently blunted the ODE-induced decrease in conduction velocity in both directions. As shown in Figure 3, longitudinal conduction velocity was increased 29±7% and 31±6% (both p<0.05 versus before sodium) 5 minutes after the end of the first and second sodium chloride boluses, respectively. In the transverse orientation, the maximum increases were observed 1 minute after the end of each bolus and were 18±5% and 21±4% (both p<0.05) after the two boluses, respectively. Conduction velocity measured in the longitudinal direction 20 minutes after the end of the first sodium chloride bolus was still 20±5% higher than that measured before sodium, whereas in the transverse direction, conduction velocity...
at 20 minutes was only 4±3% higher than before sodium chloride administration. The average change in the 20 minutes after the first bolus was greater in the longitudinal than in the transverse direction (24±5% versus 11±3%, p<0.05).

**Block of Longitudinal Conduction by High Concentrations of ODE**

Figure 4 illustrates signals recorded from each electrode in one dog at baseline, during the maintenance infusion of the low-dose and high-dose regimens, and 5 minutes after injection of a sodium chloride bolus. At the low ODE concentration (183 ng/ml), conduction slowed slightly in both directions, whereas at the higher concentration (513 ng/ml), propagation was slowed further in the transverse direction but was blocked in the longitudinal direction: The electrogram recorded from site 4 followed that from site 3, whereas the electrogram from site 2 preceded that from site 1. The electrograms from sites 1 and 2 were inverted; therefore, we conclude that impulses were initiated in the longitudinal direction at a point between sites 2 and 3. Because these records were derived by signal-averaging 10 consecutive complexes, we infer that this conduction block was stable (i.e., occurred with each beat). Administration of sodium chloride restored the normal sequence of impulse propagation in the longitudinal direction and increased conduction velocity in the transverse direction. This block of propagation in the longitudinal direction occurred in two of 11 experiments at ODE plasma concentrations ≥450 ng/ml but in none of 41 experiments when ODE concentrations were <450 ng/ml.

Serum Na⁺ and K⁺ concentrations just before the first sodium chloride bolus (140±3 meq/l and 3.4±0.1 meq/l) were not significantly different from those at baseline (141±3 meq/l and 3.4±0.1 meq/l). Peak serum Na⁺ after the first sodium chloride bolus was 160±2 meq/l at 1 minute and returned to 144±5 meq/l by 20 minutes. The second sodium bolus produced similar changes. As we have previously reported, serum K⁺ fell significantly after sodium, reaching a low value of 1.8±0.3 meq/l. Sodium boluses did not significantly change plasma ODE concentrations (464±32 ng/ml versus 420±17 ng/ml).

**Discussion**

We have previously shown that the sodium channel blockers mexiletine and quinidine, which were studied by methods similar to those described here, produce depression of conduction in both longitudinal and transverse orientations; in those experiments, depression of conduction by mexiletine (but not quinidine) was greater in the longitudinal orientation. Others have found similar results with procainamide, lidocaine, or amiodarone, although the difference between the extent of depression of longitudinal and transverse conduction is variable. We have now shown that disproportionate depression of longitudinal conduction by the class IC agent ODE occurs in a concentration-dependent fashion. Furthermore, our previous studies demonstrated that QRS and HV prolongation produced by ODE, like that produced by other sodium channel blockers such as quinidine, procainamide, or tricyclic antidepressants, can be acutely reversed by a sodium bolus. In the present study, sodium boluses acutely reversed slowing of local conduction, and this effect was more prominent in the longitudinal orientation (Figures 3 and 4).

An advantage of our methods is an electrode array specifically designed to study anisotropic conduction. We use a small number of closely spaced bipoles whose alignment can be varied, as opposed to other studies in which an array of a larger number of bipoles spaced farther apart (2.5–5 mm) is placed over an area of interest. In all these methods, the calculation of a value for conduction velocity assumes a linear and constant conduction pathway. We recognize that these methods cannot measure discontinuities at the cellular level. However, because the electrograms do not display irregular contours, the recording sites are fairly close, and we are studying normal myocardium, we believe the use of the terms \( \theta_{LONG} \) and \( \theta_{TRANS} \) are appropriate here. Another advantage of our methods is the determination of conduction at stable plasma drug concentrations. This not only allows studies of an intervention such as sodium on drug-induced conduction slowing but also permitted us to generate the concentration–response data shown in Figure 2. In a group of seven stable patients receiving long-term encainide, we found plasma ODE concentrations to vary from 63 to 381 ng/ml; plasma ODE concentrations in patients with excess sodium channel block and arrhythmias have not been reported but would presumably be higher. Thus, the concentration ranges in this report are relevant to those observed during encainide therapy.

The ionic mechanism of the effect of sodium is not known. In our previous studies, we considered the possibility that hypokalemia was responsible, perhaps by hyperpolarizing resting potential. However, the
effect of sodium boluses was reproduced even when serum K⁺ was clamped by K⁺ infusion. A second possibility is a direct effect of increased extracellular sodium on sodium current. However, in our previous studies, sodium bolus in the absence of a sodium channel blocker did not shorten QRS. Moreover, the increase in serum sodium recorded immediately after the boluses (when changes in conduction were greatest) are insufficient to produce a large change in Iₛ. It is possible that a small increase in sodium current could modulate drug binding to the channel. Such a mechanism has been proposed to explain greater sodium channel block by propafenone at low Na⁺ (70 mmol) in vitro.31 Sodium boluses produced their most prominent effects on longitudinal conduction, which is thought to be relatively more dependent than transverse conduction on sodium channel function and less on cell–cell coupling mechanisms. Thus, a direct effect of sodium boluses on sodium channel function in vivo remains one tenable explanation for these findings. However, because the effects of ODE were also more prominent in the longitudinal direction, we cannot rule out an action of sodium boluses on passive properties involved in propagation. For example, it is conceivable that the transiently increased Na⁺ activated the sodium–calcium exchange, thereby transiently decreasing [Ca²⁺], an effect that would be predicted to increase gap junction conductance.32

One setting in which conduction slowing is thought to play a prominent role in the genesis of arrhythmias is the well-recognized development of refractory sustained ventricular tachycardia during encainide or flecainide therapy.11,12 Coromilas et al33 studied the effects of flecainide in dogs with previous coronary occlusion and myocardial scars in which ventricular tachycardia was uninducible in the absence of drug. Flecainide resulted in direction-dependent conduction block, with slow conduction enabling the development of sustained ventricular tachycardia. Such nonuniform anisotropic (direction-dependent) propagation is thought to reflect barriers of collagen fibers that impair transverse conduction to a greater extent than longitudinal conduction. Nonuniform anisotropic behavior can also be observed in normal canine atria, in which rapid pacing impulses may fail to propagate in the longitudinal but continue to propagate in the transverse orientation.34 It is also conceivable that the excess mortality caused by encainide or flecainide in the Cardiac Arrhythmia Suppression Trial was related to the development of similar conduction block and subsequent arrhythmias in recently ischemic cardiac tissue.35

We found that high concentrations of ODE could, even in normal canine ventricle, result in block of impulse propagation in the longitudinal orientation. This outcome may reflect the relatively greater dependence of longitudinal than of transverse conduction on sodium channel availability. Electrograms such as those shown in Figure 4 do not allow us to delineate the pathway whereby impulses arrive between electrodes 2 and 3 in the longitudinal orientation: Propagation from transverse loci or transmyocardial conduction are possibilities. Such unidirectional block could, of course, serve to promote arrhythmias. Our finding that sodium boluses reverse this action further strengthens this hypothesis. In particular, we found that conduction was increased most in the longitudinal orientation, where it was most depressed by ODE. Thus, we believe that sodium controls arrhythmias that are caused by sodium channel blockers by preferentially enhancing longitudinal conduction, where it has been slowed to the greatest extent. The ionic mechanism underlying this beneficial action of sodium requires further study.

References

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