Electrophysiologic Effects of an Antiarrhythmic Agent, Bidisomide, on Sodium Current in Isolated Rat Ventricular Myocytes: Comparison With Mexiletine and Disopyramide

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ABSTRACT—The effects of bidisomide, an antiarrhythmic agent, on sodium current (I\text{Na}) in isolated rat ventricular myocytes were investigated using a whole cell voltage clamp method. Bidisomide blocked I\text{Na} with a K_i of 214 ± 6/d at a holding potential of −140 mV. The blockade of I\text{Na} was enhanced at a less negative holding potential of −100 mV with a K_i of 21 ± 6/d. Bidisomide shifted the steady state inactivation curve to a negative potential direction by 20 mV without a significant change in the slope factor. Bidisomide slowed the time course of recovery of I\text{Na} at a holding potential of −140 mV with a slow recovery phase. The time constant of recovery phase for bidisomide, disopyramide and mexiletine were 2703, 1858 and 757 ms, respectively. The development of the block of I\text{Na} consisted of two phases in the presence of bidisomide. The fast and slow time constants were 11 and 648 ms. Bidisomide produced a use-dependent block of I\text{Na} when the depolarizing pulse was repeated at 1 – 3 Hz. Our results indicate that bidisomide binds to rat cardiac sodium channels and that the dissociation kinetics of bidisomide from the inactivated sodium channel is slower than that of disopyramide.

Keywords: Bidisomide, Sodium current, Cardiac myocyte

An antiarrhythmic agent, bidisomide, (±)-α-{2-[acetyl(1-methylethyl)amino]ethyl}-α-(2-chlorophenyl)-1-piperidinebutanamide, was developed as an analogue of disopyramide, a class I antiarrhythmic drug. The pyridyl residue of disopyramide was replaced with a pyperidine residue in bidisomide and a halogen (chloride) was introduced to the ortho position of the benzene ring. These chemical changes produced a beneficial property; i.e., little side effect on the cardiovascular profile because of the weak negative inotropic effect and the low anticholinergic effect (1, 2). Although disopyramide is an established and widely-used class I antiarrhythmic agent, congestive heart failure and/or anticholinergic actions, such as urinary retention, dry mouth and constipation, are its side effects, which limited the clinical efficacy of disopyramide. When the negative inotropic effect was assessed in anesthetized dogs, bidisomide showed less decrease in the maximum left ventricular dP/dt than disopyramide (2, 3). Binding studies using the muscarinic radioligand [3H]-quinuclidinylbenzylate also showed that the affinity of bidisomide to the muscarinic receptor is twenty-fourfold less than that of disopyramide (2 – 4).

Bidisomide has been shown to be effective on both supraventricular (5 – 7) and ventricular arrhythmias (1, 6, 8 – 10). Although the CAST study revealed the danger of continuous use of class I antiarrhythmic drugs for patients with post-myocardial infarction with or without pumping dysfunction (11), class I drugs are still useful in eliminating ventricular and other serious arrhythmias, so the development of some sodium channel blockers without side effects is of pharmaceutical interest.

A previous experiment using guinea pig papillary muscles revealed that bidisomide decreased the maximum upstroke velocity (dV/dt max) of action potentials and shortened action potential duration (12). The decrease in dV/dt max without changing resting membrane potential strongly suggests that this agent suppresses cardiac sodium current (I\text{Na}). However, because the change in dV/dt max is not linearly related to that of I\text{Na} (13), a study recording I\text{Na} under the

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voltage-clamp condition is important to elucidate the blocking mechanism of bidisomide on cardiac sodium channels. The purpose of our study is to apply a whole cell patch clamp technique to isolated rat ventricular myocytes to assess the kinetics of bidisomide-induced block of $I_{Na}$ and to compare the recovery kinetics of bidisomide to those of other class I antiarrhythmic drugs.

In this study, we found that bidisomide had a higher affinity for the inactivated state of cardiac sodium channels. Bidisomide shifted the steady state inactivation curve to a hyperpolarizing direction and produced a use-dependent block of $I_{Na}$. Compared to other antiarrhythmic agents, disopyramide and mexiletine, bidisomide strongly slowed the recovery in $I_{Na}$ from voltage-dependent inactivation. These results indicate that bidisomide suppresses $I_{Na}$ use-dependently and exhibits a relatively slow dissociation kinetics from inactivated sodium channels.

MATERIALS AND METHODS

Isolation of myocytes

Rat ventricular myocytes were enzymatically isolated using a standard procedure (14). Briefly, rats weighing 150–200 g were anesthetized with ether, and the hearts were quickly removed and rinsed in calcium free Tyrode solution. Using a Langendorff technique, 50 units/ml collagenase (Yakult, Tokyo) was perfused approximately 15–20 min at 37°C. Ventricular muscles were minced by scissors, dispersed with gentle agitation in a KB (Kraft-brühe) medium and filtered by a 200 μm nylon mesh. Cells were stored in the KB medium. More than 80% of myocytes were rod shape and viable cells. Sixty five percent of the total isolated myocytes were tolerant to 1.8 mM extracellular calcium. Tyrode solution contained: 115.0 mM NaCl, 105.0 mM tetramethyl ammonium chloride, 5.0 mM CsCl, 0.5 mM MgCl$_2$, 5.0 mM HEPES, 1.8 mM CaCl$_2$, 0.2 mM CdCl$_2$, 4.0 mM 4-aminopyridine and 5.5 mM glucose. The liquid-junctional potential between the internal and external solutions (3.8 mV) was corrected. A T-2000 voltage clamp amplifier (Act ME, Tokyo) designed by T. Narahashi et al. was used (16). The series resistance was compensated to a point just before the value where oscillation occurred. Voltage error through the clamp circuit was considered to be within acceptable limits when the peak amplitude of $I_{Na}$ did not exceed 4 nA (17). Pulse generation and data acquisition were controlled by pCLAMP software (Axon Instruments, Foster City, CA, USA) running a Compaq PC computer, which was interfaced through a 100-kHz Labmaster board (Scientific Solutions, Mentor, OH, USA). In some experiments, the linear leakage and capacitative components of the membrane current were subtracted by the P/n (n = 5) method (18) to measure the reversal potential of $I_{Na}$. All experiments were performed at room temperature of 22–24°C.

The drug-induced changes were considered to be significant when $P$ values of ANOVA were less than 0.05. A non-linear iterative software, Igor Pro (Wave Metrics, OR, USA), was used for a curve-fitting procedure to minimize the sum of squares of the errors (19). The fitting lines in Figs. 1C, 3B, 4D and 5D were obtained with this procedure.

Chemicals

Bidisomide was a kind gift from Searle (Skokie, IL, USA); mexiletine, from Nippon Boehringer Ingelheim (Tokyo); and disopyramide, from Nippon Roussel (Tokyo). Bidisomide and disopyramide were dissolved in saline acidified with a drip of 1 N HCl and then the pH was adjusted to 7.4 with 1 N NaOH. Mexiletine was dissolved in distilled water. A stock solution (1 or 10 mM) of each drug was freshly prepared just before the experiments. The desired concentration of these drugs was obtained by diluting each stock solution.

RESULTS

Concentration-dependent effects of bidisomide on $I_{Na}$

Figure 1 shows the relationship between the unblocked fraction of $I_{Na}$ and the concentration of bidisomide. Pulses were applied to −10 mV for 30 ms from the holding potential of −100 or −140 mV every 30 s. Bidisomide was superfused in a cumulative fashion (control, 0.1, 10 μM or control, 1, 100 μM) and then washed out. As shown in Fig. 1, A and B, bidisomide decreased the amplitude of peak $I_{Na}$ in a dose-dependent manner. After washout, $I_{Na}$ almost recovered to the control value at the HP of −140 mV. In Fig. 1C, the concentration-dependent block of $I_{Na}$ is summarized. The data obtained from 4–8 experiments were fitted well by the following equation:
Fig. 1. Concentration-dependent effect of bidisomide on I_{Na}. Panels A and B: Depolarizing pulses from −140 to −10 mV for 30 ms were applied every 30 s. Current tracings are superimposed before (control), during superfusion of bidisomide (0.1 and 100 μM) and after washout at a holding potential (HP) of −140 mV (panel A) and −100 mV (panel B). Panel C. The concentration-response relationships are shown at holding potentials of −100 mV (unfilled circles) and −140 mV (filled circles). Unblocked fraction of I_{Na} was obtained from normalizing the current amplitude at control values as unity. The curves are drawn to fit the equation (see text). K_i values were 21 μM for HP of −100 mV and 214 μM for HP of −140 mV. The symbols with vertical bars represent the mean ± S.E.M. from 5–8 (HP = −140 mV) and 4–5 (HP = −100 mV) experiments.

Unblocked fraction of I_{Na} = 1 / (1 + [D] / K_i), where [D] and K_i are the concentration of bidisomide and the concentration producing a half maximal response, i.e., the apparent dissociation constant. Decrease of the holding potential from −140 to −100 mV shifts the relationship to the left. K_i at the resting state of the sodium channel (at the holding potential of −140 mV) was 214 μM. At the holding potential of −100 mV, K_i was decreased to 21 μM. In the following electrophysiological experiments, we used the concentration of 100 μM bidisomide because the holding potential must be kept at −140 mV to have sodium channels in a full resting state before the command pulses were applied and because this experimental condition was necessary for the quantitative analysis according to the modulated receptor hypothesis.

Current-voltage relationship

Typical effects of bidisomide on a current-voltage relationship are shown in Fig. 2. Depolarizing pulses of 20 ms were applied to various membrane potentials from the holding potential of −140 mV every 30 s. Under the control condition, I_{Na} was detected at the potentials positive to −70 mV, attaining the maximum value at −30 mV and reversing its polarity above 60 mV. In the presence of 100 μM bidisomide, I_{Na} was reduced by 31 ± 5% at −30 mV and 30 ± 3% at −10 mV (n = 4) without significant change in the contour of the current-voltage curves.

Effects of bidisomide on the steady state inactivation (h_v)

Effects of bidisomide on h_v were assessed by a double pulse protocol as shown in Fig. 3A. Ten-second conditioning pulses of various potentials from −140 to −40 mV were applied from the holding potential of −140 mV. After a 2.6 ms pulse at −140 mV, a 20 ms command pulse to −10 mV was applied. The protocol interval was 60 s. The h_v value was obtained from the ratio (I_{Na} at a command pulse / I_{Na} at a conditioning pulse). In Fig. 3B, the h_v values are plotted against the conditioning potentials. The curves were fitted by Boltzmann’s equation:

$$h_v = \frac{1}{1 + \exp\left((E - V_h) / s\right)}$$

where E, s and V_h denotes the potential of conditioning pulses, a slope factor, and the potential at which h_v is equal to 0.5, respectively. Bidisomide (100 μM) shifted the curves to the hyperpolarized direction by 21 ± 2 mV without a significant change in the slope factors. V_h was −75 ± 2 mV and s was 6.5 ± 0.4 under the control condition (n = 4) and changed to V_h = −96 ± 1 mV and s, 6.7 ± 0.4 in the presence of 100 μM bidisomide (n = 4).

Recovery kinetics from voltage-dependent inactivation

We used a double pulse protocol (Fig. 4A) to assess the recovery of I_{Na} from voltage-dependent inactivation. A conditioning pulse was applied from −140 to −10 mV for 5 s. After various recovery durations from 3 to 10 s at −140 mV, a command pulse was applied to −10 mV for 20 ms. This protocol interval was 60 s. Figure 4, B and C, shows superimposed current tracings elicited by command pulses with variable recovery time ranging from 3 ms to 10 s. Under the control condition, I_{Na} rapidly recovered from inactivation within 200 ms. In the presence of 100 μM bidisomide, the
time course of the recovery was prolonged.

To assess the dissociation rate of bidisomide from inactivated sodium channels, an unrecovered fraction of $I_{Na}$ was plotted against the recovery time and the relationship between the unrecovered fraction and the recovery time was fitted by a single or double exponential function, as shown in Fig. 4D. The equation for fitting was defined as follows:

$$\text{Unrecovered fraction} = A_1 \exp\left(-\frac{t}{\tau_{\text{fast}}}\right) + A_2 \exp\left(-\frac{t}{\tau_{\text{slow}}}\right),$$

where $A_1$ and $A_2$ denote constants; $t$, the recovery time; $\tau$, the time constants for the fast and slow recovery. In the control condition, the recovery process at $140 \, \text{mV}$ was fitted by a single exponential function with the time constant of $52 \pm 16 \, \text{ms}$ ($n = 5$). On the other hand, bidisomide showed double exponential changes in the recovery process adding a slower recovery phase. The dissociation rate of bidisomide from inactivated channels was estimated by this slow time constant. In the presence of $100 \, \mu\text{M}$ bidisomide, values from 5 experiments were as follows: $28 \pm 2 \, \text{ms}$ ($\tau_{\text{fast}}$), $2703 \pm 195 \, \text{ms}$ ($\tau_{\text{slow}}$), $0.71 \pm 0.10$ ($A_1$), and $0.22 \pm 0.08$ ($A_2$).

For comparison of the dissociation rate of bidisomide to other class I antiarrhythmic agents, the same protocol was used in the presence of disopyramide ($10 – 30 \, \mu\text{M}$) and...
Bidisomide attenuates the repriming of $I_{Na}$ had the fastest value of $r$ fast, but all agents added a slow phase of recovery ($r$ slow). Mexiletine had the fastest value of $r$ slow, followed by disopyramide.

The dissociation kinetics of bidisomide was the slowest among these antiarrhythmic agents.

**Time course of onset of $I_{Na}$ block by bidisomide**

The onset of block of $I_{Na}$ was assessed with a double pulse protocol as shown in Fig. 5A. The development of the block depended on the duration of the onset pulses (5 ms – 10 s), and it was assessed by the $I_{Na}$ amplitude elicited by a 20-ms command pulse at –10 mV after a 200-ms recovery interval. This protocol interval was 60 s. Figure 5, B and C, shows superimposed current tracings of $I_{Na}$ at the command pulse. Under the control condition, the onset pulses up to 1000 ms did not affect the $I_{Na}$ amplitude at the command pulse. In the presence of 100 μM bidisomide, the amplitude decreased in a double exponential fashion according to the duration of the onset pulses. In Fig. 5D, relative $I_{Na}$ from Fig. 5, B and C, was semilogarithmically plotted against the onset time, where the relative $I_{Na}$ was defined as the ratio ($I_{Na}$ at a command pulse / $I_{Na}$ at a onset pulse). The curve was fitted by the following equation:

$$
I_{Na} = A_1 \exp(-t/r_{fast}) + A_2 \exp(-t/r_{slow}) + A_3,
$$

where $A_1$, $A_2$, and $A_3$ denote constants; $t$, the onset time; and $r$, the time constants for fast and slow drug binding. The $r$ fast and $r$ slow were 11 ± 6 and 648 ± 63 ms in the presence of 100 μM bidisomide (n = 4).

**Use-dependent block of $I_{Na}$ by bidisomide**

The use-dependent effect of bidisomide was examined by repetitive application of 180 ms depolarizing pulses from –140 to –10 mV as shown in Fig. 6A. Under the control condition (Fig. 6B), the peak amplitude of $I_{Na}$ did not change after sixteen repetitive depolarizing pulses at 3 Hz. On the contrary, 100 μM bidisomide (Fig. 6: C, D and E) produced a progressive decline of the $I_{Na}$ amplitude by the 1 – 3 Hz depolarization. The magnitude of the block was enhanced by the higher frequencies of depolarization. The relative $I_{Na}$ are plotted against pulse numbers in Fig. 6F, where the $I_{Na}$ at each pulse number was normalized to the relative value with the $I_{Na}$ amplitude at the first pulse as unity. The relative $I_{Na}$ at the sixteenth pulse indicates the use-dependent effect of bidisomide at each frequency of
depolarization. The use-dependent block was enhanced by higher frequencies of depolarization. The values of relative $I_{\text{Na}}$ at the sixteenth pulse were $0.99 \pm 0.002$ (1 Hz, $n = 4$) and $0.99 \pm 0.007$ (3 Hz, $n = 5$) under the control condition. The values decreased to $0.74 \pm 0.016$ (1 Hz, $n = 5$), $0.58 \pm 0.046$ (2 Hz, $n = 5$) and $0.38 \pm 0.032$ (3 Hz, $n = 5$) in the presence of 100 $\mu$M bidisomide, showing a use-dependent block of $I_{\text{Na}}$ by bidisomide.

DISCUSSION

The present study demonstrated that bidisomide blocked $I_{\text{Na}}$ in single rat ventricular myocytes, both at resting and inactivated states of sodium channels. The dose-response relationship shifted to lower bidisomide concentrations at the less negative holding potential of $-100$ mV. Bidisomide shifted the $h_c$ curve to a hyperpolarizing direction. These results indicate that bidisomide has a higher affinity to the inactivated sodium channels than to the resting channels. We estimated the $K_i$ value of this agent for the inactivated sodium channels according to the modulated-receptor hypothesis (20, 21). In this hypothesis, sodium channels exist in resting, open and inactivated states and a drug can bind to channels in each state with a characteristic rate constant to form the drug-associated states. In the simplified analysis model, the relationship between the steady state inactivation and the dissociation constants in the channel states is described as follows:

$$dV_h = s \ln\left[\frac{1 + D/K_{i,\text{rest}}}{1 + D/K_{i,\text{inactivated}}}\right],$$

where $dV_h$ denotes the shift of the $h_c$ curve at a midpoint; $s$, the slope factor of the $h_c$ curve; $D$, the concentration of bidisomide; $K_{i,\text{rest}}$ and $K_{i,\text{inactivated}}$, the dissociation constant for resting and inactivated channels, respectively (22). We obtained values of $dV_h$, $s$, $D$ and $K_{i,\text{rest}}$ from our own experiments and $K_{i,\text{inactivated}}$ was calculated as 3.3 $\mu$M, approximately one hundred times smaller than that of $K_{i,\text{rest}}$.
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Thus, bidisomide was judged to have a higher affinity to inactivated sodium channels than to resting channels. This $K_{i,\text{inactivated}}$ value is consistent with those of previous reports that bidisomide higher than 10 $\mu M$ was needed to reduce $dV/dt_{\text{max}}$ of action potentials in guinea pig papillary muscles (12) and that bidisomide at 15 $\mu g/ml$ (55 $\mu M$) in plasma was enough to decrease the arrhythmic ratio to a half in the canine ventricular arrhythmia models (1). The arrhythmic ratio was defined as the ratio (the number of ectopic ventricular beats / the total heart rate) and it was used to show the severity of ventricular arrhythmias (1).

Use-dependent block develops when the drug-channel interaction is too slow to reach an equilibrium within a single cycle of sodium channel activation and inactivation. This type of block is important for antiarrhythmic action and explained by two different theories, the modulated-receptor hypothesis and the guarded receptor hypothesis (23). In the latter, the affinity of the drug to the binding site is constant, but the access of the drug to the binding site is guarded by activation and/or inactivation gates and the use-dependency results from the faster forward-binding rate in activated and/or inactivated states. After the removal of the inactivation of sodium channels using a chemical agent or enzyme, disopyramide and a compound similar to bidisomide were shown to reduce inactivation-removed sodium channels (24, 25), indicating these sodium channel blockers may bind to the channels at the open state. In our results (Fig. 5), the time course of the onset block of bidisomide is described with the sum of fast and slow phases. Although it is difficult to discriminate whether bidisomide binds to sodium channels at the open state or at the inactivated state, our results strongly suggest the possibility of the activated-channel blocking effect of bidisomide.

Dissociation kinetics of drugs from sodium channels is one of the important factors in the subclassification of class-I antiarrhythmic agents, because the clinical choice of the drugs is determined by referring to the dissociation time constant. In voltage clamp studies, the dissociation time constant is often represented by the recovery time constant of $I_{Na}$ as shown in Fig. 4D. To characterize the dissociation rate of bidisomide, we selected mexiletine and disopyramide, the established class I antiarrhythmic agents, and compared their values of recovery time constant (Table 1). Bidisomide has the slowest recovery time constant, fol-

![Fig. 6. Use-dependent block of $I_{Na}$ by bidisomide. Panel A shows the pulse protocol. Panels B, C, D and E: superimposed tracings of $I_{Na}$ were obtained from different experiments in the control at 3 Hz (B) and in the presence of 100 $\mu M$ bidisomide at 1 Hz (C), 2 Hz (D) and 3 Hz (E). Panel F: Relative $I_{Na}$ was plotted against each pulse number. Relative $I_{Na}$ was defined as the ratio of $I_{Na}$ at each pulse number / $I_{Na}$ at the first pulse. Unfilled and filled symbols represent the data in the absence and presence of 100 $\mu M$ bidisomide, respectively. Circles, triangles and squares represent the data at stimulation frequency of 1, 2 and 3 Hz, respectively.](image-url)
lowed by disopyramide, while mexiletine has the fastest one. Martin and Chinn (26) reported that the recovery kinetics of bidisomide was slower than that of disopyramide by using the analysis of dV/dt max reduction in guinea pig papillary muscles. In pervious voltage clamp studies, mexiletine and disopyramide slowed the time course of recovery of Ina and their time constants of the slow recovery phase were reported to be 370 and 4410 ms (24, 27). The difference of our results (mexiletine, 757 ms and disopyramide, 1858 ms) from the pervious reports may be caused by different experimental conditions including i) animal species such as guinea pig and rat, ii) pulse protocols (especially holding potentials ranging –90 to –140 mV), iii) temperature (17 – 22°C) and iv) composition of the internal and external solutions (concentration of F–/G2d, Ca2+/G2b and Cd2+/Gb0).

Unfortunately, clinical studies (11, 28) could not prove the efficacy of bidisomide in the treatment of atrial fibrillation and supraventricular tachycardia and in general that class I antiarrhythmic agents, including bidisomide, might increase the mortality during the treatment of ventricular premature beats in the patient group with prior myocardial infarction. Recently, physicians have been hesitant to use long term administration of class I antiarrhythmic agents for the prevention of ventricular arrhythmias. However, the therapy with class I antiarrhythmic agents is still indicated in the limited cases, in which the onset of serious ventricular arrhythmia is repetitive or catheter ablation therapy is unsuccessful. Bidisomide may be effective in the treatment of the arrhythmias for which other class Ia agents are effective and may be an alternative drug to disopyramide. These arrhythmias include the digitalis-induced or the catecholamine-induced arrhythmias presumed to be triggered by delayed afterdepolarizations, atrial flutter, AV node reentry, arrhythmias involving accessory pathways and ventricular tachycardias. Because of the slow dissociation from cardiac sodium channels, bidisomide might be more effective on the arrhythmias generated by intracellular Ca2+ overload than mexiletine. The reduction of the entry of sodium ion through Na+ channels may lead to the decrease of Ca2+ overload through Na+-Ca2+ exchange. Although bidisomide is currently far from the first choice of drug in the treatment of the arrhythmias mentioned above, in the case of clinical use, more attention should be paid to the proarrhythmic effects induced by its slower dissociation from sodium channels.

Limitation of our study: we followed the modulated-receptor hypothesis and analyzed the data from the whole cell voltage clamp experiment. The assumption is that the cardiac sodium channel shifts among three states; i.e., from the resting, activated to inactivated state in a voltage-dependent manner and that class I antiarrhythmic agents bind or unbind to each state of the channel with independent dissociation/association constants. In cases that there may be several inactivation sub-states to which bidisomide can bind (for example, fast and slow inactivation sub-states) and that there may be several pathways through which bidisomide can access to the channel, our results might need some corrections, because the assumption of the hypothesis would not be proper for the analysis. To address these points, further studies would be necessary using other techniques including single channel recording and electrophysiological studies on mutated sodium channels.

In summary, our results show that bidisomide may become an alternative drug with a potent blocking action of Ina in rat ventricular myocytes and that it can bind to sodium channels with slow dissociation kinetics.

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