Marked QRS Complex Abnormalities and Sodium Channel Blockade by Propoxyphene Reversed with Lidocaine

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Abstract

The opiate analgesic propoxyphene produces cardiac toxicity when taken in overdose. We recently observed a patient with propoxyphene overdose in whom marked QRS widening was reversed by lidocaine. The reversal is apparently paradoxical as both agents block the inward sodium current (I_{Na}). We examined possible mechanisms of the reversal by measuring I_{Na} in rabbit atrial myocytes during exposure to propoxyphene and the combination of propoxyphene and lidocaine (60 and 80 μM, respectively). Propoxyphene caused use-dependent block of I_{Na} during pulse train stimulation. Block recovered slowly with time constants of 20.8±3.9 s. Block during lidocaine exposure recovered with time constants of 2–3 s. During exposure to the mixture, block recovered as a double exponential. The half time for recovery during exposure to the mixture was 1.6±.9 s compared with a half-time of 14.3±2.9 s during exposure to propoxyphene alone. During pulse train stimulation, less steady-state block was observed during exposure to the mixture than during exposure to propoxyphene alone when the interval between pulses was > 0.95 s. Both drugs compete for a common receptor during the polarizing phase. The more rapid dissociation of lidocaine during the recovery period leads to less block during the mixture than during exposure to propoxyphene alone. The experiments suggest a mechanism for reversal of the cardiac toxicity of drugs which have slow unbinding kinetics.

Introduction

Propoxyphene (Darvon) is a frequently used synthetic opiate analgesic that is often implicated in drug overdose (1–4). Propoxyphene overdose causes profound cardiorespiratory and neurologic effects. While the neurologic depressant effects may be reversed by opiate antagonists, the cardiovascular effects are not favorably affected. These cardiovascular effects include widening of the QRS complex, bundle branch block, bradycardia, asystole, diminished myocardial contractility, and hypotension (5–10). Beta-1-adrenoreceptor agonists incompletely compensate for the bradycardia, conduction abnormalities, negative inotropy, and hypotension (11–13). Invasive supportive measures such as cardiac pacing are of little value (14, 15). Despite aggressive treatment, up to 76% of deaths from propoxyphene overdose in intensive care units result from cardiac toxicity (5, 6).

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We recently managed a patient with massive propoxyphene overdose who had profound central nervous system and cardiac toxicity with convulsions, respiratory depression, bradycardia, marked QRS widening, and hypotension. The bradycardia but not the QRS abnormality was reversed by epinephrine. We made the empiric observation that lidocaine administration repeatedly narrowed the widened QRS complex. Prompted by the clinical observation, we performed a review of the basic pharmacology of propoxyphene. Preclinical studies had shown that the parent drug and its major metabolite norpropoxyphene are potent local anesthetics (16, 17). The local anesthetic effects of propoxyphene and norpropoxyphene were not reversed by the opiate antagonist naloxone. They depress action potential $\dot{V}_{max}$ at concentrations that may be realized during clinical toxicity (17). Furthermore, the intravenous administration of toxic doses of propoxyphene and norpropoxyphene to rabbits produced electrocardiogram (EKG) changes consistent with conduction depression (18).

Recent theoretical and experimental studies suggest the combination of two sodium channel blockers that have markedly different binding kinetics may under some circumstances produce less sodium channel blockade than that produced by one of the pair of drugs (19–23). A drug with rapid association and dissociation kinetics may displace a drug with slower binding kinetics. Therefore we explored this possibility as the basis for the lidocaine-propoxyphene interaction by performing sodium current measurements in rabbit atrial myocytes under voltage clamp. We were able to show that propoxyphene is indeed a potent Na channel blocker that dissociates from the sodium channel at about one tenth the rate of lidocaine. Less steady-state block of the sodium current was observed during pulse train stimulation in the presence of propoxyphene and lidocaine than propoxyphene alone when the interval between pulses was > 0.95 s. The experiments suggest that lidocaine may under certain circumstances reverse the cardiotoxic effects of propoxyphene that result from sodium channel blockade.

Methods

Patient description. A 35-yr-old woman was admitted to the intensive care unit of Durham County General Hospital after taking on overdose of propoxyphene in a suicidal attempt. She was unconscious and seizing at the time of presentation. Her blood pressure was 130/94 and heart rate 102/min. Despite a transient response to naloxone boluses of 4 and 10 mg, and a continuous naloxone infusion of 3 mg/h, coma deepened, and she required mechanical ventilation for acute respiratory failure. Gastric lavage was performed and activated charcoal was administered per nasogastric tube. Initial studies included a drug screen and a 12-lead electrocardiogram. The drug screen revealed a propoxyphene level of 14.6 μg/ml (toxic level > 2 μg/ml) and traces of a tricyclic antidepressant. Her clinical course was dominated by seizures and signs of cardiac toxicity. The seizures did not respond to lorazepam and drug loading regimen with phenytoin 25 mg/min was initiated. This was terminated after 450 mg had been administered

because of progressive hypotension. A dopamine infusion was initiated in an attempt to control the hypotension. A norepinephrine infusion was added and the rate adjusted to keep the blood pressure at 80/50 (final infusion rate 15 μg/ml). The QRS duration which was 100 ms on her admission EKG (Fig. 1 *A*) widened progressively, her systolic blood pressure fell to 40 mmHg and the heart rate decreased to 50/min. Epinephrine 0.5 mg i.v. increased the heart rate, but did not restore the QRS duration to normal (Fig. 1). Lidocaine 100 mg i.v. was given empirically and the QRS complex transiently narrowed. Another bolus of lidocaine, 100 mg, was given with normalization of the QRS complex. Her blood pressure stabilized at 90/50. Over the next 3 h, the QRS duration again markedly widened and the heart rate dropped to 30 bpm. The bradycardia was reversed by epinephrine 0.5 mg i.v., but the QRS remained widened. A third bolus of lidocaine was administered with prompt narrowing of the QRS complex. The same sequence of events was again observed and a maintenance infusion of lidocaine 2 mg/min was administered after the fourth intravenous bolus of lidocaine. The patient's clinical status slowly improved and the lidocaine infusion was discontinued after 12 h. The patient recovered completely after 72 h and she was transferred to the psychiatric unit.

In vitro experiments. Atrial cells were obtained from the hearts of 2.5–3.5 kg rabbits. Each heart was perfused by the Langendorf technique with an enzyme medium as previously described (24). The enzyme medium consisted of collagenase 180 U/ml (Worthington Biochemical Co., Freehold, NJ) and hyaluronidase 10 mg/100 ml (Sigma Chemical Co., St. Louis, MO) in Krebs-Henseleit (K-H) solution. After 30–40 min of perfusion, the heart was placed in K-H solution containing 10% FBS, streptomycin 0.5 U/ml, and penicillin G 1 U/ml. The K-H solution contained (mM): NaCl 118.2, $CaCl_2$ 2.7, KCl 4.7, $MgSO_4 \cdot 7H_2O$ 1.2, $NaHCO_3$ 25, NaH_2PO_4 1.2, glucose 11. The enzymatically digested atria were separated from the ventricles, minced into 2–4 mm sections and exposed to elastase 0.5 mg/ml dissolved in Ca^{2+} free K-H solution. The dissociation of the segments was closely monitored by microscopic examination of small aliquots of cell-containing medium at 5-min intervals. The individual cells were isolated by filtration. Atrial cells were plated onto 18 × 18 laminin-coated coverslips and cultured at 37°C in an incubator with a 5% CO_2 enriched humidified atmosphere. Culture medium consisted of Ham's F12 and Dulbecco minimal essential medium (DMEM) in a 1:1 ratio and 10% fetal bovine serum. Culture medium also contained streptomycin 0.5 U/ml and penicillin G 1 U/ml. The atrial cells were elongated when freshly isolated and became spherical after 24–48 h in culture. Spherical cells were selected for study as they had a capacity of 15–35 pF allowing a fast, stable voltage clamp. Cells were kept in culture 2–5 d before use.

On the day of study, a coverslip containing cultured cells was placed in a recording chamber on the stage of an inverted microscope (Nikon Diaphot; Nikon Inc., Garden City, NJ). The recording

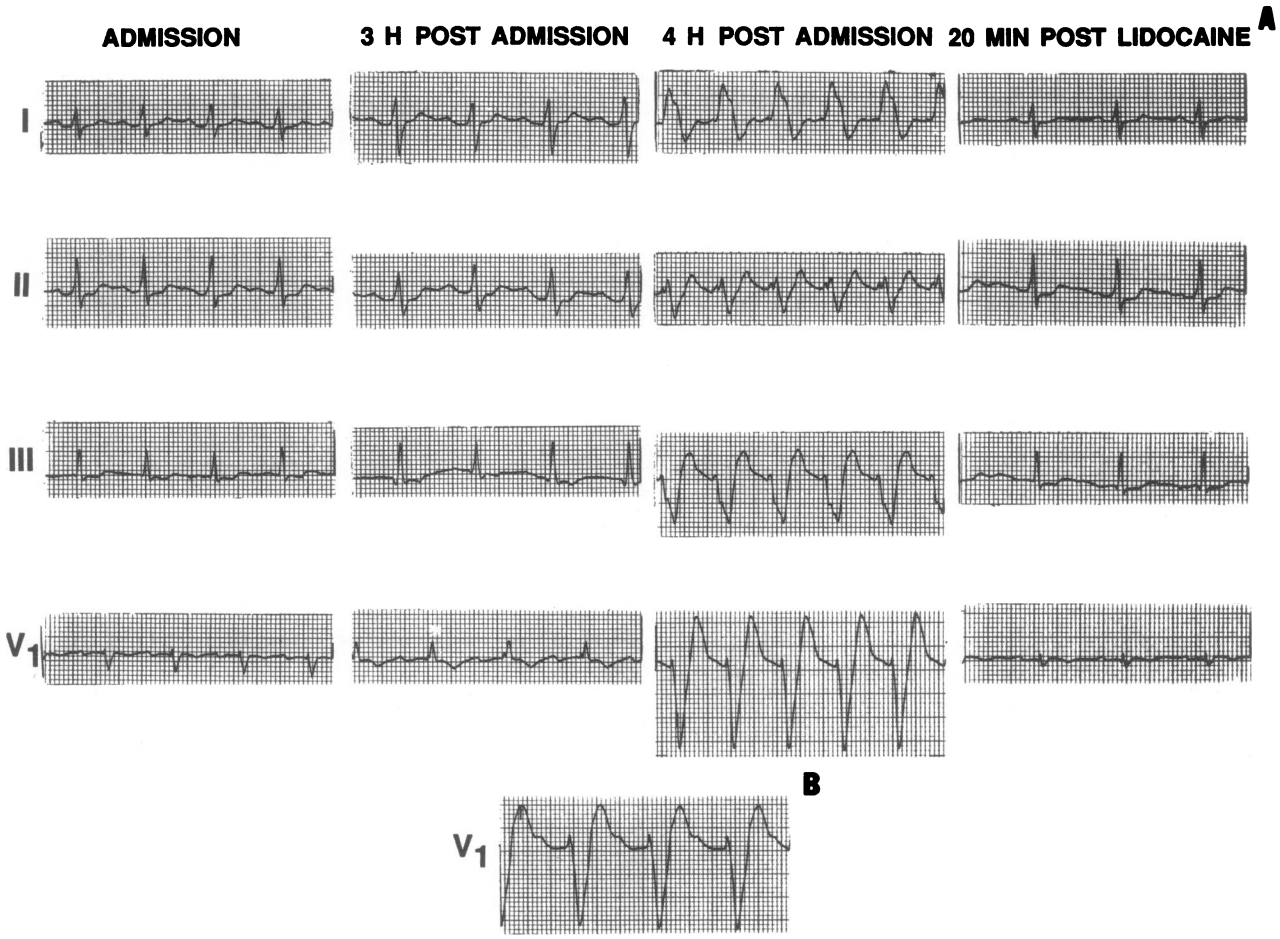

Figure 1. Electrocardiograms obtained from patient B.E. during a hospital admission for propoxyphene overdose. (*A*) EKG leads I, II, III and V_1 obtained at the time of admission, 3 h postadmission, 4 h postadmission, and 20 min later after the administration of 100-mg bolus of lidocaine. The admission EKG shows 1st degree A-V block (PR interval, 0.22 s) and a normal QRS duration (0.1 s). 3 h later, the PR interval was 0.24 s, the QRS duration 140 ms and the terminal forces in lead V_1 were now directed anteriorly. The EKGs in the third column of A were taken after the administration of 0.5 mg i.v. epinephrine. A wide QRS complex tachycardia is now present (QRS duration, 0.17 s), and the mean frontal plane axis is now leftwards. 20 min after lidocaine administration, PR and QRS duration are normal (fourth column). (*B*) A segment of lead V_1 with sinus rhythm, 1st degree A-V block, and marked QRS prolongation (QRS duration 200 ms). This record was obtained before another episode of bradycardia and marked QRS widening.

chamber was cooled to 15°C with a peltier-based temperature control device (TS-4 thermal microscope stage; Sensortek, Clifton, NJ). The cells were superfused at a rate of ~ 1 ml/min with a solution containing (mM): NaCl 75, CsCl 75, $MgCl_2$ 1, KCl 5, $CaCl_2$ 1.5, glucose 5, and Hepes 10. The pH was adjusted to 7.4 using HCl or CsOH. The external superfusate solution also contained lidocaine 80 μM, propoxyphene 60 μM (Sigma Chemical Co.) or a combination of propoxyphene 60 μM and lidocaine 80 μM. The cells were allowed to equilibrate with the external solution for at least 30 min.

Microelectrodes of resistances 400–1,200 KΩ were made using either a vertical micropipette electrode puller (model 750; David Kopf, Inc., Tujunga, CA) or a Flaming-Brown horizontal puller (model P80/PC; Sutter Instruments Co., San Rafael, CA). The microelectrodes were pulled from borosilicate glass with an outside diameter of 1.5 mm (N-51A; Drummond Scientific, Broomall, PA). The micropipettes were filled with an internal solution containing (mM): CsCl 60, CsF 60, $MgCl_2$ 5, K_2(ATP) 5, KH_2PO_4 1, EGTA 5, glucose 5, and Hepes 10, and the pH was adjusted to 7.3 with CsOH or HF.

Microelectrodes were coupled to a patch-clamp amplifier, either an EPC 7 (List Electronics, Darmstadt, West Germany) or an Axopatch 1 B (Axon Instruments, Inc., Burlingame, CA) through an Ag/AgCl wire. The command pulses were generated with an IBM-XT (IBM Corp., Armonk, NY) microcomputer, a TL-1 interface (Axon Instruments, Inc.) and a custom software program designed to run the experimental protocols as a batch file from the fixed disk drive of the computer.

Whole-cell currents from the recording chamber were either recorded on an analogue tape recorder (model 4DS; Racal Instruments, Vienna, VA) at 30 in./s using "wideband 1" with an effective band width of DC-20 KHz or were directly digitized using a custom software program written in "C" programming language, a Compaq 386 20 mHz microcomputer (Compaq Computer Co., Houston, TX) and a data translation analog to digital interface board (DT2821 input-output board; Data Translation, Marlboro, MA). Records directly digitized were filtered at 5 KHz before digitizing using an 8-pole Bessel filter (model 902; LPF Frequency Device, Inc., Haverhill, MA).

To record whole cell sodium currents, a giga-ohm seal was obtained on a suitable cell using the method described by Hamill et al. (25). The capacitive transient of the amplifier input and the microelectrode were nulled and the cell membrane ruptured by a pulse of suction. The additional capacitive transient from the cell was nulled and the cell holding potential was lowered to −120 mV. A current-voltage relationship was performed by applying 20-ms pulses at 1,500-ms intervals incrementing the amplitude by 5 mV. The peak current was used to calculate the voltage error due to uncompensated series resistance. We compensated for 50–90% of the series resistance using analogue circuitry and would only proceed with the experiment if the voltage error was < 3.5 mV. If threshold phenomena were observed in the negative limb of the current voltage-relationship the experiment was abandoned. Once a stable seal with appropriate control was demonstrated, one of the following protocols was initiated.

Train protocol. The development of frequency dependent block was determined by the application of trains of 50-ms pulses with interpulse intervals of 0.1, 0.15, 0.45, 0.95, 1.95, 2.95, 3.95, and 4.95 s. There were 50 pulses of 0.1, 0.15, 0.45, 0.95 interpulse interval and 40 pulses of 1.95, 2.95, 3.95, 4.95-s interpulse interval. We used fewer pulses at the longer cycle length as steady-state block is achieved with a smaller number of pulses (26). Between each train there was a 90-s rest interval.

Recovery protocol. The rate of recovery from block was determined by the application of a train of 40 conditioning 50 ms pulses to −20 mV with a 150-ms inter-pulse interval. This was followed by a variable recovery period and a 10-ms test pulse to −20 mV was used to assess available sodium current. The recovery periods evaluated were 0.250, 1, 5, 10, 30 and 60 s in propoxyphene. In the propoxyphene-lidocaine combination, points at 0.5, 3, and 15 s were evaluated in addition to those above. Between each test pulse and the succeeding train there was a 90-s rest interval.

The recovery and or pulse train protocol was applied during exposure to propoxyphene alone. The superfusate was then changed to one containing a combination of propoxyphene and lidocaine. After 15 min of exposure to the combination, the initial protocol was repeated. Because of the long recovery intervals required in the stimulation protocols and 15-min drug exposure, we were usually not able to do both sets of observations in the same cell. The currents were therefore normalized against the peak value of current obtained in a given condition. As the results will demonstrate, the drug interaction could be clearly demonstrated despite this difficulty.

Data analysis. Data on analogue tape was digitized at 20 KHz after filtering at 5 KHz with an 8 pole Bessel filter (model 902; LPF Frequency Devices, Inc., Haverhill, MA) and stored on the fixed disk drive of a Compaq 386 microcomputer using custom software. The digitized data were transferred to a SUN 4/280 minicomputer (SUN Microsystems, Inc., Mountainview, CA) where the peak values of the individual current traces were determined using software developed in our laboratory. These peaks were plotted and exponentials were fitted to the data describing the recovery from, or development of block using the Marquardt procedure (27). Where single exponentials did not provide a good fit, we used two exponentials to characterize the kinetics.

Results

The hallmark of the blocking action of the local-anesthetic class of sodium channel blockers is use- and frequency-dependent block (28–30). Fig. 2 shows that 60 μM propoxyphene shares these properties. Panels A–C show the sodium currents from every 4th pulse from trains of 50 (C) or 40 (A and B) 50-ms pulses to −20 mV from a holding potential of −120 mV. The interpulse interval was 1.95, 0.95, 0.1 s in A, B, and C, respectively. At each pulse interval, there was a progressive decline in current during the pulse train. The 40 or 50 pulses during the train were sufficient for steady-state block to be achieved. The level of steady-state block increased as the interval between pulses was decreased. D summarizes data on

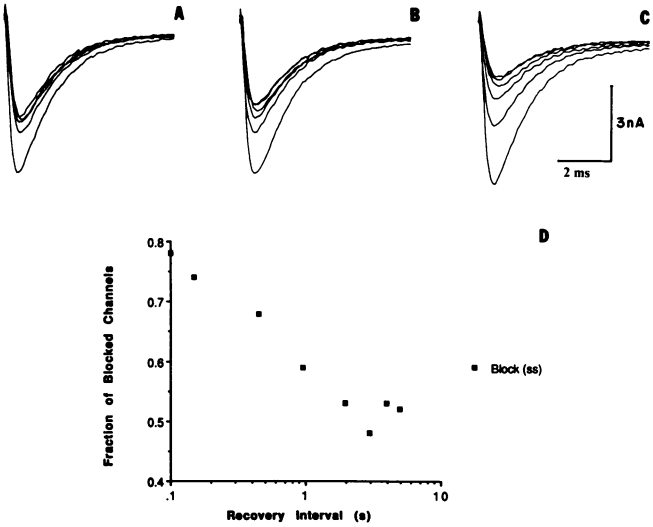

Figure 2. Use-dependent block of the sodium current during exposure to 60 μM propoxyphene. (*A–C*) Sodium channel currents recorded from an isolated atrial myocyte with the holding potential set at −120 mV and trains of 50-ms pulses to a test potential of −20 mV applied with interpulse intervals of 1.95, 0.95, and 0.1 s, respectively. Only every 4th pulse in each train is shown. The current and time calibrations shown in C also apply to the current traces in A and B. The fractional block of the sodium current is plotted as a function of the interval between pulses (recovery interval on a logarithmic scale) in D.

the steady-state level of block as a function of the interpulse interval in nine cells. The summary data confirm the results from the single experiment in A–C: steady-state level of block increased as the interpulse interval decreased.

The progressive decline in sodium current during pulse-train stimulation results from enhanced binding of propoxyphene to a sodium channel receptor(s) during the depolarizing pulse. This enhanced binding may be the result of differential affinity of drug with the various states of the channel, and or differential access to guarded binding sites of fixed affinity (28, 29, 31). Some block dissipates between the pulses as drug dissociates from the channel during the interpulse period. The rate of this dissociation or recovery process is an important determinant of the overall blocking process. If the interpulse interval is less than approximately four recovery time constants, block accumulates until the amount of block gained during a pulse is equal to that lost during the recovery interval. The fact that we observed cumulative block with pulse intervals as long as 4.95 s suggest that propoxyphene dissociates slowly from the sodium channel at 15°C. We set out to determine the kinetics of this recovery process using two approaches.

Recovery from block. We examined the kinetics of recovery from block at −120 mV by introducing test pulses of varying coupling intervals at the end of a blocking train of 40 pulses of interpulse interval 150 ms. The coupling interval of the test pulse was varied from 0.25 to 60 s. A recovery period of 90 s separated the test pulse and the next blocking train. Fig. 3 shows the results of one of these experiments during exposure to 60 μM propoxyphene. As the coupling interval was increased, the current during the test pulse increased progressively. The recovery process could be fitted by a single exponential with a recovery time constant of 19.2 s. In nine cells, the time constant of recovery was 20.8±3.9 s. This approach of determining the recovery time constant is generally not applicable to providing an estimate in the in vivo situation where the long recovery pauses are not practical.

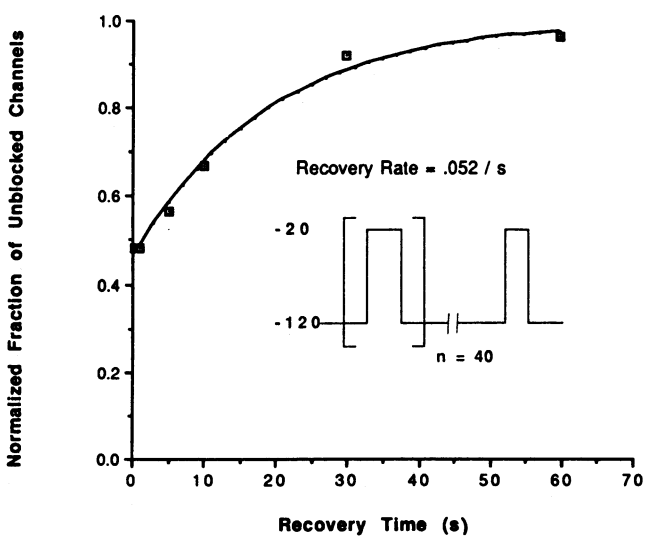

Figure 3. Recovery from block during exposure to 60 μM propoxyphene. Block was induced with a train of forty 50-ms pulses from a holding potential of −120–−20 mV. After a recovery period of 0.24 s or greater, test pulses to −20 mV were applied. There was a rest period of 90 s between the test pulses and subsequent blocking trains. The pulse protocol is shown in the insert. The recovery from block was fitted with a single exponential with a recovery rate constant of 0.52/s (time constant 19.2 s).

We had previously shown that it is possible to obtain time constants for the binding of drugs to the various states of the sodium channel from the responses to pulse-train stimulation (26). In our original description, we had considered binding to a single state during the depolarized phase of the pulse, and unbinding from a single state during recovery period between pulses. Block during a train developed as a piecewise exponential process with a rate that was inversely proportional to interpulse interval. By application of trains of pulses of fixed duration at various rates, it was possible to determine binding and unbinding parameters of drug to its receptor. In subsequent studies, we have shown that by varying both the interpulse interval and the duration of the pulse, it was possible to obtain binding rate constants to the multiple states that may more accurately describe channel binding during the pulse. The methods are very general, and are not dependent on the precise mechanism for the change in binding during the pulses i.e. change in receptor access or change in affinity nor on the specific channel gating model. In this section, we illustrate the use of the method to describe the recovery time constant during propoxyphene exposure.

We have plotted the peak value of the sodium current during a train of 50-ms pulses in a propoxyphene-exposed cell in Fig. 4 *A*. A single exponential provided a good fit to the points. The rate constants determined from similar curves are plotted as a function of the interpulse interval in Fig. 4 *B*. There is a linear relationship between the uptake rate and the interpulse interval. From the slope of this relationship, we calculated a recovery time constant of 22 s. With this method we obtained a mean of 24.6±7.9 s from a total of 15 experiments. This value is not significantly different from that obtained with single test pulses ($P > 0.05$).

These time constants measured for propoxyphene are much longer than those reported for lidocaine. Sanchez-Chapula, Tsuda, and Josephson reported a time constant of recovery from lidocaine block of 400–600 ms at room temperature (~ 24°C) in rat ventricular myocytes (32). Bean, Cohen, and Tsien observed recovery time constants of 1–2 s at 16.6°C in rabbit Purkinje fibers (33). The long time constants during propoxyphene exposure are consistent with the cumulative block observed even at long interpulse intervals. If both lidocaine and propoxyphene share a common binding site, they would compete for available binding sites during the pulses. During the diastolic period the rapid dissociation of lidocaine may result in a net decrease of overall blocking at some interpulse intervals during exposure to both blockers. We tested these ideas by examining the recovery from block and the response to pulse train stimulation during exposure to propoxyphene and a mixture of both agents.

Fig. 5 shows the result of an experiment in which both protocols were performed. During exposure to propoxyphene alone, the sodium current recovered as a single exponential with a time constant of 15 s. The preparation was then exposed to the combination of propoxyphene and lidocaine for 20 min and the protocol repeated. During exposure to both drugs, the sodium current recovered faster than during exposure to propoxyphene alone. The sodium current recovery was best fitted by a double exponential with time constants of 2.2 and 18.8 s. These two time constants are similar to those observed during exposure to lidocaine and propoxyphene, respectively. For comparison of the overall recovery process, we calculated the

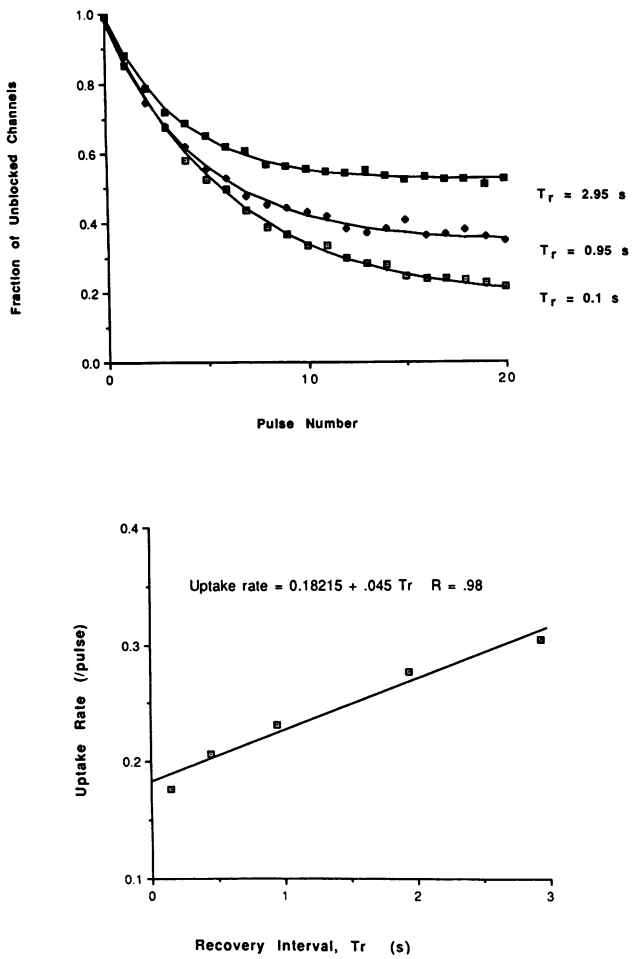

Figure 4. Determination of recovery time constant from block using the kinetics of current decline during pulse train stimulation. (*A*) Normalized currents from representative pulse trains with interpulse intervals of 0.1, 0.95, and 2.95 s. The continuous lines show single exponential fits to the declining current. In B, the rate constants for the decline in current are plotted against the interval between pulses (recovery interval). The recovery time constant was estimated from the slope of the least squares straight line. The estimate of the recovery time constant was 22 s.

half-times ($t_{1/2}$) observed during exposure to propoxyphene alone and those during exposure to the mixture. $t_{1/2}$ was 14.3±2.9 s (n = 7) during exposure to propoxyphene alone, and 1.6±0.9 s during exposure to the mixture (n = 7).

We examined the steady-state level of block over a range of interstimulus intervals in cells during exposure to propoxyphene alone and propoxyphene and lidocaine. The results of one experiment is summarized in Fig. 6. At interstimulus intervals of less than 0.95 s, greater block was observed during exposure to the combination of propoxyphene and lidocaine than to propoxyphene alone. At interstimulus intervals greater than 1 s less steady-state block was observed during exposure to the combination of the two drugs. Similar results were observed in two other cells.

Discussion

Clinical presentation. The case we have presented highlights many of the problems associated with propoxyphene toxicity. Many of the effects mediated through its action on the opioid receptors ($\delta > \mu > \kappa$) are reversed by naloxone or are readily treated, e.g., mechanical ventilation for acute respiratory failure. The cardiovascular complications present a greater therapeutic challenge. The mortality rate from a group of 222 patients treated for propoxyphene overdose in one intensive care unit was 7.7%, over three times that of tricyclic overdoses treated in the same medical center (34). These patients rarely died from respiratory complications. Instead, the most serious problems were cardiovascular, accounting for 13 of 17 (76%) deaths.

The major cardiovascular complications are disturbances of rhythm and hypotension. These may be delayed as the propoxyphene metabolite norpropoxyphene is 2.5 times more potent than the parent compound in producing cardiac depression. Cardiac complications were delayed in our patient. Her heart rate and QRS duration were normal at the time of admission. However, her heart rate slowed and the QRS duration increased over the ensuing 4 h. The rhythm disturbance in our patient was primarily sinus bradycardia. The electrocardiogram in Fig. 1 *A* (third column) shows a wide QRS complex tachycardia. This EKG was obtained after the administration

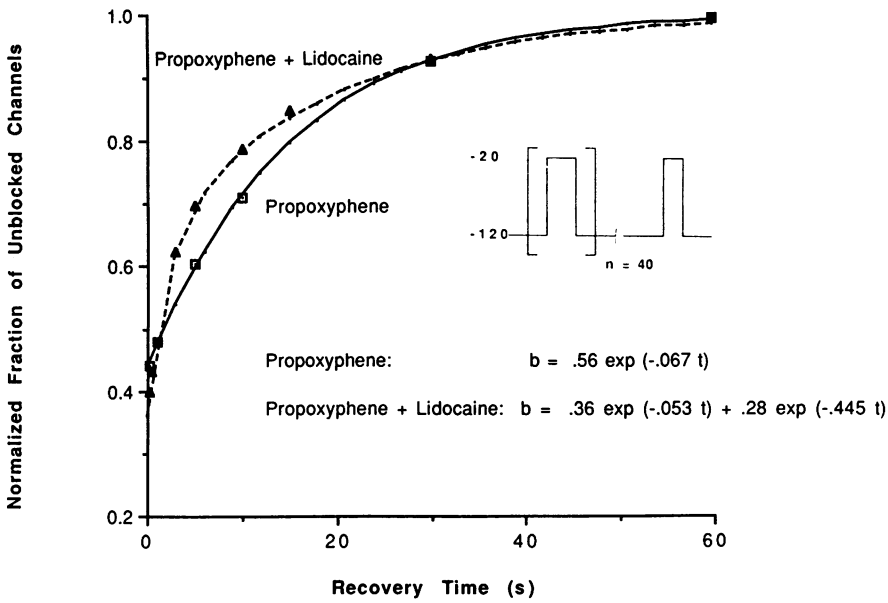

Figure 5. Recovery from block (*b*) during exposure to propoxyphene alone and propoxyphene and lidocaine. The pulse protocol is the same as that used in Fig. 3 and is shown in the insert. During exposure to propoxyphene alone, the sodium current recovered as a single exponential with a rate constant of 0.067/s (time constant 15 s). Recovery during exposure to the mixture of propoxyphene and lidocaine was best fitted by a double exponential with recovery rate constants of 0.053 and 0.445/s (time constants 18.8 and 2.2 s).

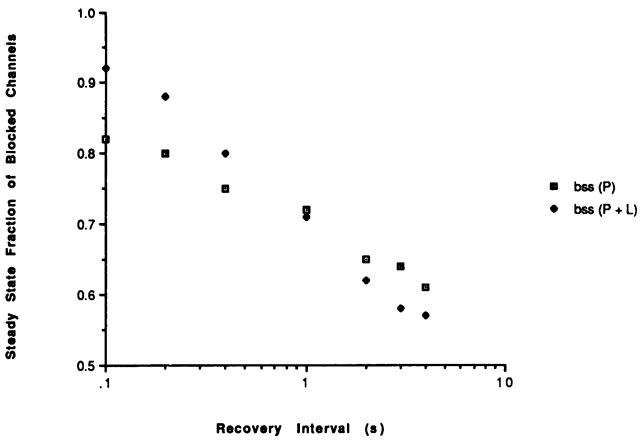

Figure 6. Fractional block of the sodium current with pulse train stimulation during exposure to propoxyphene alone and a mixture of propoxyphene and lidocaine. The fraction of blocked channels is plotted on the ordinate, the recovery interval between pulses is plotted on the abscissa. For intervals greater than 1 s, less block is observed during exposure to the combination of propoxyphene and lidocaine than to propoxyphene alone.

of epinephrine. P waves are not clearly visible. The differential diagnosis was between ventricular tachycardia and supraventricular tachycardia with aberrant conduction. Other episodes of wide QRS complex tachycardia that followed epinephrine injection were presaged by sinus bradycardia, 1st degree A-V block, and marked QRS prolongation. This suggests that slowing of conduction was at least partly responsible for the rhythm disturbances.

The bradycardia and QRS widening observed during propoxyphene overdose result from the blockade of cardiac membrane sodium channels. Experiments in nerve and cardiac muscle indicate that propoxyphene and norpropoxyphene are potent sodium channel blockers. Propoxyphene was more potent than lidocaine, quinidine, and procainamide in this regard (17). In our patient, we observed narrowing of an abnormally prolonged QRS duration by lidocaine administration repeatedly. Though dilantin may have contributed to the QRS narrowing, we doubt that its presence contributed significantly as a therapeutic level was not achieved or maintained and it was discontinued before the QRS widening. We did not consider restoration of a normal QRS duration an isolated therapeutic objective. However, because a markedly prolonged QRS duration may portend the development of serious arrhythmias, we eventually treated the patient with a constant infusion of lidocaine. Normal QRS duration was maintained once the infusion was started. It was this observation that motivated the in vitro experiments that we discuss below. The bradycardia may result from blockade of the inward calcium current. We are not aware of any studies actually demonstrating this effect.

The other major cardiovascular complication of propoxyphene overdose is hypotension. Hypotension is usually a late complication of toxicity with the naturally occurring opiates such as morphine (33). It may be more prominent in the early course of toxicity with the synthetic narcotic analgesics such as propoxyphene. The hypotension is relatively refractory to adrenergic and dopaminergic agonists. For example, systolic blood pressure was 70–80 mmHg in our patient during infusion of norepinephrine 15 μg/min and dopamine 8 μg/kg per min. There are probably two mechanisms for this effect. Both propoxyphene and norpropoxyphene are negative inotropic agents (10, 17). They also cause relaxation of vascular smooth muscle. These actions may result from blockade of the calcium current. Beta 1-adrenergic agonists may partially reverse these complications by increasing the calcium current.

Effects of propoxyphene on the sodium current. We explored the mechanism of QRS widening by propoxyphene and the reversal by lidocaine by measuring the inward sodium current in atrial myocytes under voltage clamp. At the present time, it is generally not possible to voltage clamp the inward sodium current under the conditions of temperature and electrolyte concentration obtained in vivo. We reduced the temperature to 15°C, to separate the capacitive and ionic currents at depolarized potentials. The lowered temperature is known to shift the gating variables of the sodium current to more hyperpolarized potentials (35). We routinely used the relatively hyperpolarized potential of −120 mV to remove resting sodium channel inactivation. The magnitude of the sodium current was reduced by decreasing the external sodium concentration from 150 to 75 mM. This increased the likelihood of obtaining adequate voltage control of the inward sodium current. Although we did not attempt to determine the adequacy of voltage control by using a second microelectrode outside the voltage clamp circuit, other criteria suggested adequate voltage control (36). We selected ionic conditions such that the peak early currents recorded were carried by sodium ions. The concentrations of propoxyphene and lidocaine we used were in the toxic range. They were selected to obtain enough sodium channel blockade such that the kinetics of blockade could be analyzed quantitatively. Because of these recognized shortcomings of current voltage clamp technique, we limited our objectives to the following two questions: (*a*) Does propoxyphene depress the inward sodium current in a frequency dependent manner when measured under voltage clamp? (*b*) Are there conditions under which less sodium current blockade can be observed during exposure to the combination of propoxyphene and lidocaine than propoxyphene alone?

The experiments show that propoxyphene produced use dependent block of the inward sodium currents at interpulse intervals of 0.1 to 4.95 s. The block of the sodium current at interpulse intervals as long as 4.95 s is consistent with a slow dissociation of propoxyphene from its binding site(s) on the sodium channel. Measurement of the time constants of recovery from block directly, or estimates based on the decline of the sodium current during pulse train stimulation confirm the slow recovery from block. Vaughan Williams has recently pointed out that there is a high degree of correlation between the time constant of recovery from block and the rate of development of block duration pulse train stimulation (37). Drugs fall into three broad classes with rapid, intermediate, and slow onset and recovery from block. Propoxyphene falls in the intermediate class, while lidocaine falls in the rapid class.

Effects of the combination of propoxyphene and lidocaine on the sodium current. During exposure to the combination of propoxyphene and lidocaine the recovery process was biexponential. The half times during exposure to the combination were shorter than during exposure to propoxyphene alone. From the shorter half times, one would predict that at least at some interpulse intervals, less block would be observed during exposure to the combination of propoxyphene and lidocaine than to propoxyphene alone. We were able to confirm this prediction in three sets of experiments. One would predict less

slowing of conduction and hence narrowing of the QRS complex at those rates where less block is observed in the combination of drugs. We believe these experiments illustrate part of a broader underlying principle.

When two drugs compete for the same receptor site, one expects binding in excess of that associated with either agent alone. The basis for this property is that both agents have continuous access to a common receptor. The binding events result from collisions between the drug and the receptor so that the presence of the two drugs will increase the collision rate and thus the fraction of bound sites. In the case of the sodium channel, there is generally a direct relationship between receptor occupancy and the decline in the sodium current. Multiple intermediate steps between channel blockade and the decline in current do not appear to be involved. Partial agonists are not well defined in this system. However, because net drug binding occurs only transiently during pulse train stimulation, additive blocking by a combination of two drugs no longer applies under all conditions. The steady-state level of block during pulse train stimulation is no longer easy to predict since net binding and unbinding is determined by the kinetics of interaction of each drug with the common receptor, and the duration of the respective binding and unbinding intervals (19). During the interval of net binding, both drugs compete for the receptor with rates determined by their respective binding constants. During the interval of net unbinding (diastolic interval between pulses), those channels blocked by a fast recovery drug such as lidocaine will become unblocked much quicker than those blocked by a drug with slow kinetics such as propoxyphene. Therefore, the fraction of blocked channels just before the next stimulus may be reduced by competition between a blocker with slow unbinding kinetics and another blocker having much faster kinetics. The net result is an apparent paradoxical decline in block in the presence of the combination of drugs. At short unbinding (recovery) intervals where little unbinding of both the fast and the slow agent has occurred, only a net increase in block can be expected.

The principles as we have outlined apply equally well to sodium channel models that assume a common binding site(s). Models based on variations of binding due to changes in channel state (e.g., the modulated receptor model described by Hondeghem and Katzung and Hille), or variation binding due to change in drug access to the putative binding site (e.g., the guarded receptor model proposed by Starmer et al.) can accommodate the proposed interaction.

To our knowledge, Rimmel et al. were the first to demonstrate an apparent paradoxical effect of a combination of sodium channel blocking agents. In three experiments, they observed less decrease in $\dot{V}_{max}$ recorded from frog node of Ranvier during exposure to the combination of benzocaine and procaine than to procaine alone (20). Benzocaine has much faster binding and unbinding kinetics than procaine. In a subsequent study, they also demonstrated the apparent paradox during exposure to the combination of benzocaine and lidocaine (21). In this case, lidocaine was the agent with slower kinetics. These results were extended by Chapula in a study in guinea pig papillary muscles using $\dot{V}_{max}$ (22). He observed a recovery time constant of 26 ms during exposure to benzocaine and 127 ms during exposure to lidocaine alone. Less block was observed with pulse train stimulation during exposure to the mixture of benzocaine and lidocaine than during exposure to lidocaine alone. Clarkson and Hondeghem showed an apparent paradoxical effect of a combination of lidocaine and bupivacaine on $\dot{V}_{max}$ in guinea pig ventricular muscle (23). They showed that at stimulus rates < 4 Hz, a smaller decrease of $\dot{V}_{max}$ was observed during exposure to the combination of bupivacaine and lidocaine than to bupivacaine alone. That study was motivated by the observation that the local anesthetic bupivacaine precipitated serious arrhythmias and death if accidentally injected by an intravascular routine. Their study pointed to a potential beneficial effect of lidocaine in bupivacaine-induced arrhythmias. To our knowledge such benefit has not been documented in a clinical arrhythmia. Bennet, Woosley, and Hondeghem have recently described the converse problem (38). They presented the case of two patients in whom a dose of lidocaine that was initially effective lost its effectiveness with time. Using whole-cell sodium channel measurements, they were able to show competition between lidocaine and its metabolites for sodium channel receptor. Under some pulsing conditions less sodium channel block was observed in studies of the drug combination.

In our study, we were able to show that the rate of recovery from block during exposure to the combination of propoxyphene and lidocaine was faster than that during exposure to propoxyphene alone. At interpulse intervals of > 0.95 s, less steady-state block was observed during exposure to combination of propoxyphene and lidocaine than to propoxyphene alone. We believe that the case presentation and the subsequent experiments illustrate the principle of the apparent paradoxical effect of a combination of sodium channel blocking agents. We would stress that the voltage clamp experiments do not reproduce the conditions under which the clinical observations were made. The object of the experiments was to determine if we could illustrate the principle underlying the clinical observation. As such, we think these objectives have been achieved in this study. The rate of recovery of the sodium channel from block by drugs depends critically on pH, external potassium and membrane potential (30). The effect of potassium may result largely from its effect on membrane potential. The precise conditions of heart rate, extracellular potassium and pH under which an apparent paradoxical effect may be observed will require further experiments in vivo and the in situ heart.

A proarrhythmic effect of antiarrhythmic drugs has been recognized in a significant percentage of patients treated with these agents. The effects appear to be particularly prominent with the class I C drugs. The primary approach to treatment of the drug-induced arrhythmias is discontinuation of the offending drug. As a group, the class 1 C drugs have slow binding kinetics. The class I B drugs such as lidocaine and dilantin have fast binding kinetics and could potentially reverse the proarrhythmic effects of the class I C agents. The usefulness of such a strategy would need documentation with in vitro and in vivo experiments. The strategy of treating with a second drug with faster kinetics would be useful in circumstances where the clinical situation warrants other treatment in addition to discontinuing the proarrhythmic drug.

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