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Torsade de Pointes With an Antihistamine Metabolite: Potassium Channel Blockade With Desmethylastemizole

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Objectives. **Proarrhythmic effects have been observed with the selective histamine$_1$ (H_1) receptor antagonist drug astemizole, a widely prescribed antihistamine. The metabolites of astemizole and those of other antihistamine compounds have not been implicated as causative agents of cardiac arrhythmias. The purpose of this study was to examine whether desmethylastemizole, the principal metabolite of astemizole, blocks delayed rectifier potassium (K^+) channels.**

Background. **QT interval prolongation and torsade de pointes are associated with astemizole intake and have been ascribed to block the repolarizing K^+ currents, specifically the rapidly activating component of the delayed rectifier iKr. Astemizole undergoes extensive first-pass metabolism, and its dominant metabolite, desmethylastemizole, has a markedly prolonged elimination time. We report the clinical observation of QT prolongation and torsade de pointes in a patient with undetectable serum concentrations of astemizole (<0.5 ng/ml) and "therapeutic" concentrations of desmethylastemizole (up to 7.7 ng/ml or 17.3 nmol/liter).**

Methods. **The perforated patch clamp recording technique was used to study the effects of desmethylastemizole (20 nmol/liter) on action potentials and iKr in isolated rabbit ventricular myocytes.**

Results. **Desmethylastemizole produced action potential prolongation and the induction of plateau early afterdepolarizations. Under voltage clamp conditions, desmethylastemizole suppressed iKr amplitude by ~65%. The drug E-4031 (100 nmol/liter), which selectively blocks iKr, had a similar effect on current amplitude.**

Conclusions. **Desmethylastemizole, the major astemizole metabolite, blocks the repolarizing K^+ current iKr with high affinity. The clinical observation of QT prolongation and torsade de pointes found with astemizole intake may principally be caused by the proarrhythmic effects of its metabolite desmethylastemizole.**

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Astemizole (Hismanal) is a second-generation selective histamine$_1$ (H_1) receptor antagonist prescribed for symptomatic relief of allergic rhinitis. Several reports of QT interval prolongation and torsade de pointes associated with astemizole intake have appeared. The clinical circumstances where this proarrhythmic effect has occurred include exposure to high doses of astemizole (1), concomitant administration of other QT prolonging drugs (2,3) and the presence of a congenitally prolonged QT interval (4). The occurrence of QT interval prolongation and torsade de pointes with astemizole and other selective H_1 receptor antagonists has been attributed to blockade of potassium (K^+) currents (5–7). Specifically, astemizole has been demonstrated to block K^+ channels that carry the rapidly activating, delayed rectifier K^+ current (iKr) (5). Although potential proarrhythmic effects have been observed with the parent compound, the metabolites of astemizole and other antihistamine compounds have not been implicated as causative agents of cardiac arrhythmias.

In this study, we describe a patient who developed QT prolongation, recurrent episodes of torsade de pointes and cardiac arrest after taking the recommended daily dose of astemizole. The arrhythmias were associated with undetectable blood concentrations of the parent drug and "therapeutic" concentrations of its major metabolite, desmethylastemizole. We used these clinical observations to test the hypothesis that desmethylastemizole is a potent blocker of iKr.

Methods

Clinical data. The patient was admitted to the coronary care unit at the University of Wisconsin Hospital and Clinics. Continuous telemetry, as well as 12-lead surface electrocardiograms (ECGs), was digitally recorded on standard equipment (Hewlett-Packard). The QT interval was measured to the final return of the repolarization wave to baseline from recordings obtained at 25 mm/s paper speed. Because the patient was in chronic atrial fibrillation and the QT interval is rate dependent, the QT interval was assessed by measuring the shortest and the longest QT intervals from the same ECG limb lead (standard ECG lead III) at comparable ventricular rates. QT

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Abbreviations and Acronyms

EAD = early afterdepolarization
ECG = electrocardiogram, electrocardiographic
H_1 = histamine$_1$
IC_{50} = concentration for half-maximal drug block
iKr = delayed rectifier K^+ current

nterval measurements were made by one of the authors (T.J.H.) who had no knowledge of the time and the clinical setting of the recording. Routine laboratory data were obtained through the hospital clinical laboratory. Serum astemizole and desmethylastemizole concentrations were determined by a high performance liquid chromatography assay utilizing electrochemical detection (National Medical Services). The lower limit of detection was 0.5 ng/ml for astemizole and for its major metabolite, desmethylastemizole.

Single cell data. *Single rabbit ventricular cell isolation procedure* Rabbit ventricular cells were isolated using the method previously developed in this laboratory (8). Briefly, the rabbits (weighing 2 to 3 kg) were anesthetized with ketamine hydrochloride (80 to 100 mg/kg body weight intramuscularly), xylazine hydrochloride (3 to 5 mg/kg intramuscularly) and sodium pentobarbital (50 mg/kg intravenously) before excision of the hearts. The heart was perfused by means of aortic cannulation with normal Tyrode's solution for 4 min. This was followed by 5 min of perfusion with nominally calcium (Ca^{2+})-free Tyrode's solution, and a final perfusion of 8 min with Tyrode's solution containing albumin (1 mg/ml), protease (0.05 mg/ml) and collagenase (0.6 mg/ml). The ventricles were cut into small pieces and incubated in fresh enzyme solution containing collagenase (1 mg/ml) and protease (0.1 mg/ml) for 10 min at 37°C while being agitated in a shaking water bath. The isolated cells were filtered through a nylon mesh (210 μm) and stored in a solution containing (in mmol/liter) 130 potassium glutamate, 5.7 $MgCl_2$, 0.1 EGTA and 10 HEPES.

Perforated patch-clamp recording technique. Action potentials and membrane currents were recorded in whole-cell configuration using the amphotericin B–perforated patch method as described by Rae et al. (9) (see also Zhou et al. [8]). This method minimizes cell dialysis and permits the stable recording of membrane currents and cell contraction (8). Amphotericin B (60 mg/ml) was dissolved in dimethyl sulfoxide and then added to an internal pipette solution at a final concentration of 240 μg/ml. The internal pipette solution contained (in mmol/liter) 100 potassium glutamate, 40 KCl, 1.0 $MgCl_2$ and 10 HEPES and was titrated with KOH to pH 7.2. Access resistance for voltage clamp experiments was 8 to 12 MΩ. With electronic series resistance compensation (typically 70% to 80%) in these cells, the voltage error during peak K^+ current should be ~1 mV. The external solution contained (in mmol/liter) 137 NaCl, 4.0 KCl, 1.8 $CaCl_2$, 1.0 $MgCl_2$, 10 glucose and 10 HEPES (pH 7.4). A Dagan 3900 patch clamp amplifier was used to record action potentials and ionic currents. Computer software (pCLAMP) was used to generate voltage clamp protocols as well as to record action potentials and ionic currents. The data were stored in the computer for later analysis. All experiments were performed at 36 ± 1°C.

Action potentials were recorded using the current-clamp mode. To study delayed rectifier K^+ currents in voltage clamp, sodium current was voltage inactivated by holding cells at −40 or −50 mV, and L-type calcium current was blocked by adding 1 μmol/liter nifedipine and 10 μmol/liter cadmium.

Drugs. Astemizole and desmethylastemizole were obtained from Research Diagnostics Incorporated. The purity of each drug was >99.8%. Each drug was dissolved in ethanol to give a stock concentration of 10 mmol/liter. E-4031, which selectively blocks iKr, was obtained from Eisai Ltd. (Ibaraki, Japan) and was dissolved in distilled water to give a stock solution of 1 mmol/liter.

Statistical methods. Results are expressed as mean value ± SE. Differences between means were evaluated by the use of a paired *t* test or a repeated measures analysis of variance, where appropriate. A p value ≤0.05 was considered significant.

Results

Clinical findings. An 81-year old woman presented after an episode of sudden collapse at a church meeting. Bystanders initiated cardiopulmonary resuscitation, and paramedics, who arrived within 8 min, found the patient in ventricular fibrillation. She was converted with a single 200-J external defibrillation shock to atrial fibrillation with a moderate ventricular response and transported to the hospital in a hemodynamically stable condition. Past cardiac history was remarkable for chronic atrial fibrillation and long-standing hypertension. Medications on admission included a hydrochlorothiazide/triamterene preparation, digoxin, aspirin and astemizole 10 mg/day on an as-needed basis. Initial laboratory test results revealed a serum K^+ concentration of 3.6 mEq/liter and a magnesium concentration of 1.8 mEq/liter; her electrolyte, cardiac muscle enzyme and liver function test results were normal. The serum digoxin concentration was 0.7 ng/ml. The ECG on admission showed atrial fibrillation with a varying ventricular response rate (average 88 beats/min) without conduction abnormalities or acute ischemic changes. The QT interval ranged from 600 ms (shortest) to 640 ms (longest).

The patient remained in atrial fibrillation throughout her hospital course. During the first 48 h of recovery in the coronary care unit, several spontaneous episodes of self-terminating torsade de pointes were recorded, as shown in Figure 1. One episode degenerated into ventricular fibrillation, which was promptly defibrillated. At the time of onset of this arrhythmia, telemetry monitoring showed the patient to be in atrial fibrillation with an average ventricular response rate of 84 beats/min, and the measured QT interval over 30 s varied between 580 ms (shortest) to 680 ms (longest). The episodes of torsade de pointes subsided after the administration of intravenous magnesium sulfate and additional K^+ supplementation, and by 48 h after admission no further occurrences of torsade de pointes were recorded. Within 4 days, the patient's

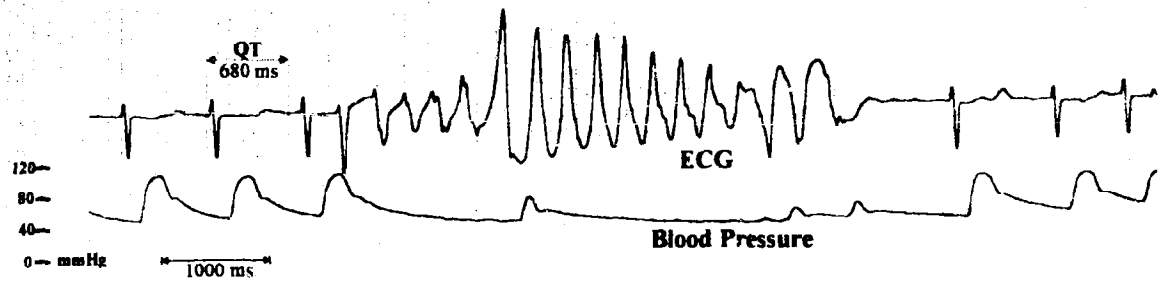

Figure 1. Torsade de pointes on an electrocardiographic (ECG) recording. The **upper trace** shows a telemetry strip recording with the longest QT measured at 680 ms. The radial pulse pressure is shown on the **lower trace.**

mentation had returned to normal from an initial postarrest hypoxic encephalopathy. Coronary angiography showed no significant coronary artery disease. Echocardiography revealed normal systolic ventricular function, increased atrial size, mild mitral regurgitation and moderate concentric left ventricular hypertrophy. At the time of discharge (9 days after admission), the QT interval varied from 440 ms (shortest) to 560 ms (longest) at an average ventricular response rate of 90 beats/min. At 3 months' follow-up, the QT interval recorded on the ECG had normalized and varied between 360 ms (shortest) and 400 ms (longest) during atrial fibrillation at an average ventricular response rate of 82 beats/min.

The history of astemizole intake in this patient prompted the determination of parent drug and principal metabolite concentrations in blood samples drawn on admission and on the fourth day in the hospital (after spontaneous episodes of torsade de pointes had resolved). Neither serum sample contained a measurable quantity of astemizole. The concentrations of desmethylastemizole were 7.7 ng/ml (17.3 nmol/liter) on admission and 2.0 ng/ml on the fourth hospital day. The "normal" ranges of steady-state plasma concentrations after a 10-mg daily dose of astemizole were 0.1 to 1.4 ng/ml for astemizole and 0.8 to 10 ng/ml for desmethylastemizole (10). A combined total concentration of more than ~20 ng/ml is considered toxic (National Medical Services).

Patch clamp studies in isolated heart cells. The effect of desmethylastemizole on properties of action potentials was studied in isolated rabbit ventricular cells. Figure 2 shows results from one cell. A control action potential is shown at the left. Exposure to 20 nmol/liter of desmethylastemizole resulted in the development of action potential prolongation (second action potential), followed by the induction of early afterdepolarizations (EADs) arising from voltages close to the action potential plateau (third action potential). Washout of desmethylastemizole resulted in the disappearance of EADs and the gradual return of action potential properties toward control conditions (right action potential). Desmethylastemizole had no effect on the rest potential (−83.0 ± 1.8 mV for control, −82.7 ± 2.0 mV for cells just before induction of the first EAD, n = 5 cells, $p > 0.05$) or action potential amplitude (128.7 ± 2.3 mV for control, 130.1 ± 1.9 mV for cells just before induction of the first EAD, n = 5 cells, $p > 0.05$). Under the same conditions, action potential duration at 50% of repolarization was increased from 273 ± 44 ms for control conditions to 439 ± 49 ms just before the initiation of the first EAD (n = 5 cells, $p < 0.05$). In these cells, the time range required to induce EADs with desmethylastemizole exposure was 7 to 20 min. In addition to provoking single EADs, desmethylastemizole occasionally caused multiple EADs before cell repolarization (data not shown). We also studied the parent drug astemizole (10 nmol/liter) in two cells. At this concentration it resulted in action potential prolongation and the induction of plateau EADs (data not shown), similar to previous findings of Salata et al. (5).

Figure 3A shows voltage clamp data obtained with 20 nmol/liter of desmethylastemizole. Families of current traces from one cell obtained for control conditions and after 12 min of exposure to desmethylastemizole are shown in the upper part of the figure, with the voltage clamp protocol shown above the current traces. In each recording the holding potential was −40 mV, and depolarizing steps were applied to voltages between −30 and +30 mV at 10-mV increments. For control conditions, depolarizing steps activated a time-dependent,

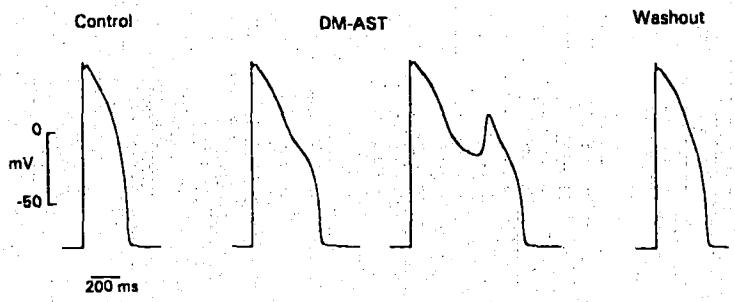

Figure 2. Induction of action potential prolongation and EADs by desmethylastemizole (DM-AST) in a single rabbit myocyte. The cell was stimulated at 0.5 Hz. The **left** action potential was recorded in control solution. The **middle** action potentials show that desmethylastemizole (20 nmol/liter) increased action potential duration and induced plateau EADs. The **right** action potential was recorded after desmethylastemizole washout for 20 min.

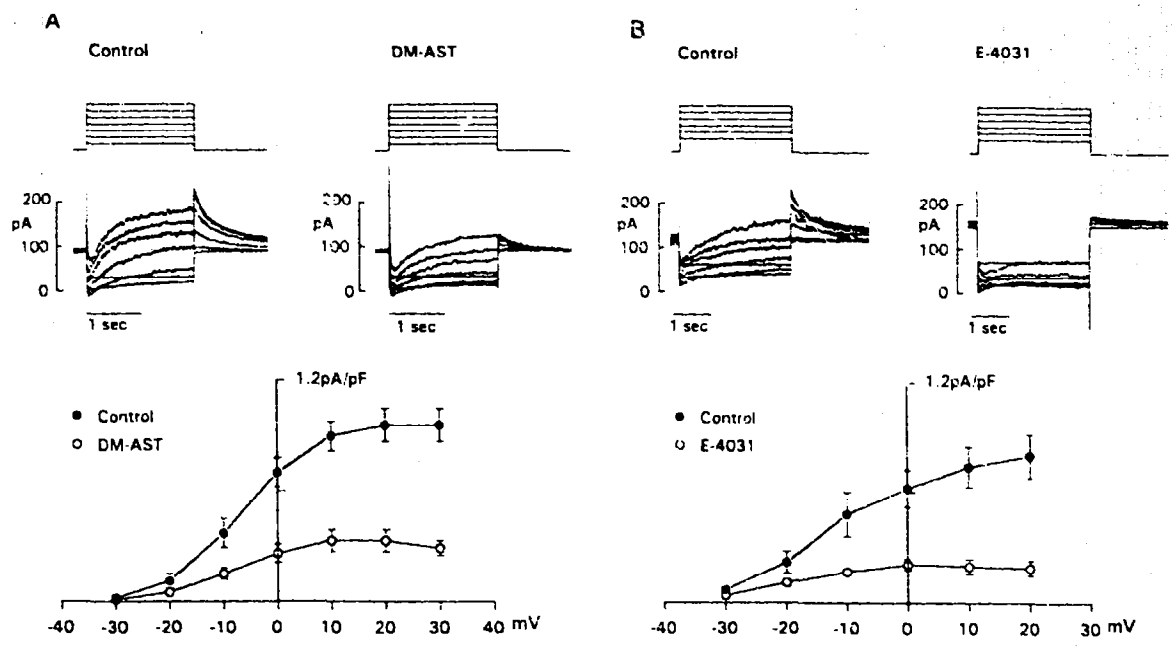

Figure 3. Effect of desmethylastemizole and E-4031 on iKr in rabbit ventricular myocytes. **A and B**, Records of iKr currents recorded in control solution and in the presence of 20 nmol/liter of desmethylastemizole (DM-AST [A]) or 100 nmol/liter of E-4031 (**B**). The cells were held at −40 or −50 mV and clamped at 10-mV increments to voltages between −30 and +30 mV (desmethylastemizole) or −30 and +20 mV (E-4031). The current–voltage plots show similar suppression of iKr tail current amplitude by desmethylastemizole and E-4031.

outward K^+ current that increased in amplitude at more positive voltages. After the repolarizing step to −40 mV, an outward tail current was recorded. Tail current amplitude initially increased after more positive depolarizing steps, but after voltage steps to +10, +20 and +30 mV, the K^+ currents were superimposed. Desmethylastemizole (20 nmol/liter) suppressed both the outward current during depolarizing steps and the tail current. Figure 3A also shows current–voltage plots of tail current peak amplitude normalized to cell capacitance for six cells. For control conditions (filled circles), the threshold for activating delayed rectifier K^+ current was close to −30 mV, and maximal activation was obtained at voltages near +20 mV. In the presence of desmethylastemizole (open circles), peak tail current amplitude was significantly reduced compared with control conditions after repolarizing voltage steps ($F_{(1,69)} = 199$, $p < 0.001$). After the return step from +20 mV, where tail current amplitude was maximal, desmethylastemizole reduced the peak current amplitude by 65%. This reduction in iKr with desmethylastemizole suggests that it may be slightly less potent than astemizole, for which the concentration for half-maximal drug block (IC_{50}) for blockade of iKr is reported to be 1.5 nmol/liter (0.7 ng/ml). In three cells, washout of desmethylastemizole resulted in the return of tail current amplitude nearly to the control level (data not shown). Similar findings were obtained using a holding potential of −50 mV.

The delayed rectifier K^+ current in rabbit ventricular cells is nearly completely suppressed by the experimental antiarrhythmic drug E-4031, and it rectifies inwardly at very positive voltages, hence it is thought to represent iKr (11–14). To confirm this in our experimental model, we studied drug block by E-4031. Figure 3B shows voltage clamp data obtained with 100 nmol/liter of E-4031. In the upper part of the figure, families of current traces from one cell are shown for control conditions and after exposure to E-4031, with the voltage clamp protocol shown above the current traces. Depolarizing steps were applied to voltages between −30 and +20 mV at 10-mV increments, and elicited a time-dependent, outward K^+ current, followed by a tail current after the return step to the holding potential. E-4031 (100 nmol/liter) suppressed both the outward current during depolarizing steps and the tail current, consistent with block of iKr. Figure 3B also shows current–voltage plots of tail current amplitude normalized to cell capacitance for three cells. When compared with control data (filled circles), in the presence of E-4031 (open circles), peak tail current amplitude was significantly reduced after repolarizing voltage steps ($F_{(1,24)} = 100$, $p < 0.001$). After the return step from +20 mV, E-4031 reduced the peak tail current amplitude by 75%. At a higher concentration of 1 μmol/liter (n = 3 cells), E-4031 reduced the peak tail current amplitude by 95% (data not shown). We conclude that the delayed rectifier K^+ current we recorded has properties similar to iKr, as reported previously in rabbit ventricular cells (11–13).

Discussion

Therapy with the selective H_1 receptor antagonists astemizole and terfenadine (Seldane) has been associated with QT prolongation and torsade de pointes, usually in the setting of

supratherapeutic doses or elevated serum concentrations. The clinical findings in this study demonstrate QT prolongation with the induction of torsade de pointes and cardiac arrest that occurred in the presence of "therapeutic" serum concentrations of desmethylastemizole and undetectable (<0.5 ng/ml) serum concentrations of the parent compound, astemizole. Moreover, the results of this study demonstrate that desmethylastemizole potently blocks iKr, which, in isolated cells, resulted in action potential prolongation and induction of EADs. At 20 nmol/liter, iKr amplitude was reduced by more than 50%. The drug concentration we studied was similar to the patient's measured serum concentration; thus, desmethylastemizole blocks iKr at concentrations that have been considered therapeutic. We conclude that this in vitro action of desmethylastemizole may underlie the proarrhythmic effects we observed in vivo.

Our results are the first to show that desmethylastemizole blocks iKr, and they are different from previous findings obtained with the H_1 receptor antagonist, terfenadine. The parent compound, terfenadine, as with astemizole, has been shown to block iKr (5,7), whereas the principal metabolite, terfenadine carboxylate, is inactive against K^+ channels (7). Similar findings with terfenadine and its metabolites have been reported for cloned K^+ channels (15,16).

In the patient we described, several conditions were present that may have favored the development of desmethylastemizole-induced long QT syndrome and torsade de pointes. The patient was taking a thiazide diuretic and she had a serum K^+ concentration close to the lower limit of normal (17). The presence of left ventricular hypertrophy also may enhance the induction of EADs (18). Similarly, atrial fibrillation with associated varying cycle lengths and action potential durations may predispose the ventricle to the induction of EADs and torsade de pointes. The presence of a congenital long QT syndrome is unlikely given the normal QT interval on follow-up electrocardiography and the absence of previous ventricular arrhythmic events or sudden death in the patient or family members.

Astemizole is rapidly and completely absorbed after oral administration. Three major metabolites (desmethylastemizole, norastemizole and 6-hydroxydesmethylastemizole), which are more potent histamine antagonists than astemizole, are generated in humans (10,19,20). Of these, desmethylastemizole is the dominant metabolite (10) being produced by oxidative demethylation of astemizole through the hepatic cytochrome P450 system (CYP2D6). Desmethylastemizole normally achieves a higher serum concentration than that of the parent drug because of extensive first-pass metabolism of astemizole (10,21). After a single dose of astemizole, as well as after the discontinuation of chronic dosing, the serum concentration-time curve of desmethylastemizole exhibits a biphasic decay with an initial phase half-life of 1 to 2 days and a prolonged terminal phase elimination half-life of ~9 to 13 days (10). Thus, complete elimination of desmethylastemizole requires several weeks. The serum concentration-time curve of astemizole also exhibits a biphasic decay; however, in contrast to its desmethyl metabolite, it decays more rapidly with the initial half-life of decay reached within a few hours and a terminal elimination phase half-life of 1.1 days (10).

Clinical implications. There are important clinical implications to our findings. Astemizole and terfenadine are commonly prescribed drugs, with over 2.5 million astemizole prescriptions filled in 1995 in the United States (22). Both astemizole and terfenadine have been reported to cause QT prolongation and torsade de pointes, and both of these compounds have been shown to block delayed rectifier K^+ channels. Terfenadine's metabolites do not block K^+ channels; thus, it is only the parent compound that is electrophysiologically active and has proarrhythmic activity. For astemizole, the parent compound and its principal metabolite, desmethylastemizole, block the delayed rectifier K^+ current and induce action potential prolongation and EADs, as we have shown. Thus, both drugs may contribute to QT prolongation and the development of torsade de pointes. However, because of the extensive first-pass metabolism of astemizole to desmethylastemizole, and because of the prolonged elimination time of desmethylastemizole, it becomes the predominate circulating compound after astemizole administration. The clinical observation of QT prolongation and torsade de pointes found with astemizole intake may principally be caused by the proarrhythmic effects of its metabolite, desmethylastemizole. Hence, the biotransformation of astemizole into an electrophysiologically active metabolite with a long elimination time may be an undesirable pharmacologic property.

Study limitations. In the patient in our report, we cannot exclude that some electrophysiologic effects resulted from low concentrations of astemizole that were not detected by the assay we used. However, because the IC_{50} for astemizole blockade of iKr is reported to be 0.7 ng/ml (5), and because the patient's arrhythmias lasted for 48 h and QT prolongation persisted for many days, the likelihood that the parent compound contributed to the patient's arrhythmias is small. Finally, other membrane currents were not studied; therefore, additional drug effects cannot be excluded.

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