QT Interval Prolongation and Atypical Proarrhythmia: Monomorphic Ventricular Tachycardia with Trimebutine

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Abstract: A 59-year old woman was admitted at emergency for palpitation and dizziness. Medication history showed trimebutine 450 mg daily, because of meteorism, increased to 450 mg TID a week earlier. At admittance, sustained monomorphic ventricular tachycardia was interrupted by 100 mg intravenous lidocaine and a largely prolonged QTc (523 ± 12 ms) was seen. Discontinuation of trimebutine achieved normalisation of QTc (420 ± 10 ms, $p<0.001$).

This is the first report in man to illustrate a probable proarrhythmic action of trimebutine. A weak inhibitory effect on both rapid and slow components of the delayed rectifier in guinea-pig ventricular myocytes calls for further investigations in human myocardial tissues. Trimebutine inhibition of Na^+ and Ca^{++} channels in cardiac tissues of rabbits and guinea-pigs also call for further studies in human myocardial tissues.

Keywords: Trimebutine, proarrhythmia, prokinetic agents, QT prolongation, ventricular tachycardia, delayed rectifier K^+ current.

QT interval prolongation is a well known cause of arrhythmia which may be also accounted for by a large variety of drugs affecting action potential duration (APD) in myocardial tissues [1-3]. Some class III agents and other drugs, particularly in guinea-pig hearts [4], by affecting separate components of the delayed rectifier K^+ current [respectively rapid, I(Kr) and/or slow, I(Ks) components], may prolong APD and QT interval which may interfere with their anti-arrhythmic capabilities or even cause arrhythmias [5, 6]. These effects were seen with azimilide or combined dofetilide and HMR 1556 [5] and with the prokinetic agent cisapride, the latter inhibiting I(Kr) with an IC_{50} of 15 nmol/L which is about 1/3 to 1/15 of the therapeutic levels [6]. Thus several cardiac [1-3] and non-cardiac [7] drugs have a hidden pro-arrhythmic danger accounting for prolonged QT in patients who may later present with life-threatening arrhythmias, including both monomorphic ventricular tachycardia (VT) [8-11] and, more frequently, *torsade de pointes* (TdP). Among non-cardiac agents, a strong case was made years ago with common histamine H_1 receptor antagonists such as the non sedating agent terfenadine, which prompted important changes acted by regulatory Agencies in pre-registration requirements [2, 12].

There are several commonly used drugs to regulate motility in the gastrointestinal tract of which cisapride [13-16] has long been reported to provoke potentially life-threatening arrhythmias including monomorphic VT and TdP. We describe here the occurrence of QT interval prolongation and monomorphic VT during oral administration of the prokinetic agent trimebutine (brand name: Debridat). Although a depressant effect on sinus node pacemaker activity of the rabbit [17] and a weak inhibitory effect on both I(Kr) and I(Ks) in guinea-pig ventricular myocytes [18] were reported with trimebutine, this is the first report in man to illustrate a proarrhythmic action, probably due to toxicity. On the other hand, similar to a previously reported case of a patient with human immunodeficiency virus infection and clarithromycin administration, it is illustrated that drug-induced long QT may be in conjunction with monomorphic VT [9], which might be less unusual than previously thought [1, 7, 8, 10, 11].

CASE REPORT

A 59-year old woman presented at emergency with palpitation and dizziness. She had a previous history of mitral valve replacement for rheumatic disease ten years earlier and had chronic atrial fibrillation (AF). A more recent angiography showed normal coronary arteries and good overall contractility and no ventricular hypertrophy. She had no family history of syncope, sudden death, or known long QT syndrome and was followed-up in our outpatient clinic where digoxin, diuretics and acenocumarol were prescribed. At last visit, two weeks earlier, she was in NYHA class I and apart from AF the ECG was unremarkable. At emergency, the ECG showed monomorphic sustained VT (Fig. **1**) which was interrupted by the intravenous administration of 100 mg lidocaine. The ECG recorded immediately after VT interruption showed a prolonged QTc at 523 ± 12 ms by Bazett's formula (Fig. **2**). Thereafter, continuous monitoring

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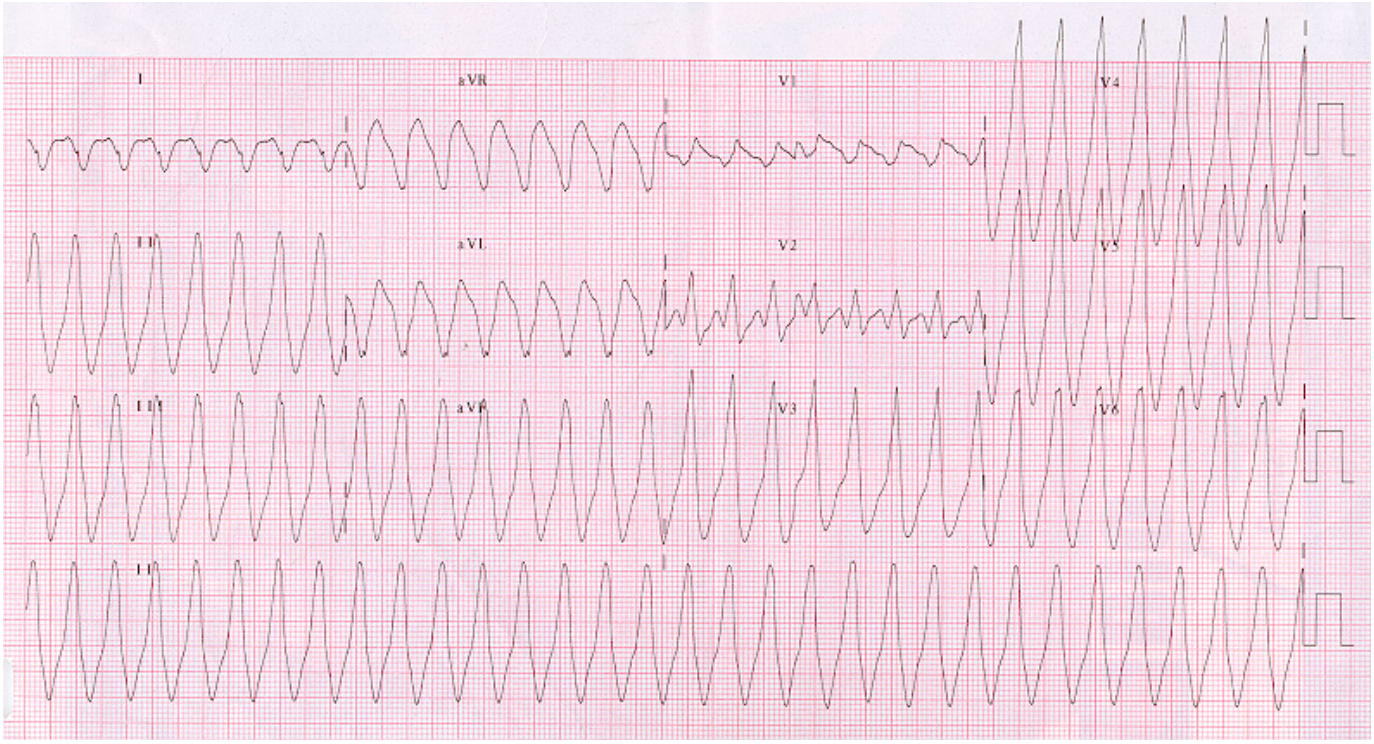

Fig. (1). Standard ECG recorded at patient's admittance showed monomorphic sustained VT.

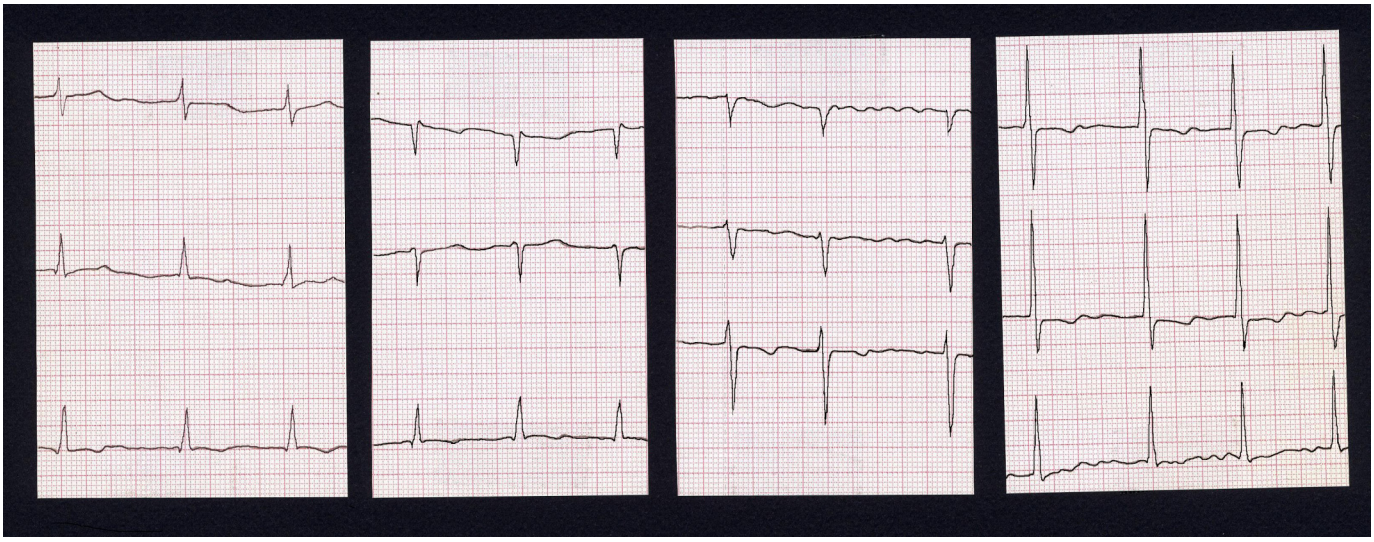

Fig. (2). After intravenous administration of 100 mg lidocaine monomorhic sustained VT was interrupted. This ECG was recorded immediately after VT interruption and shows atrial fibrillation (which was chronic in this patient). QTc obtained with Bazett's [2] formula was extremely prolonged at 523 ms (average QT = 480 ms; average RR = 840 ms). Average QTc, measured using several complexes was 523 ± 12 ms.

of ECG showed premature beats and short runs of VT (data not shown).

Serum electrolytes, creatinine clearance and digoxin plasma levels were normal. At careful medication history, it was ascertained that a general practitioner prescribed trimebutine, 450 mg daily (3 pills of 150 mg), because of meteorism. However, the patient decided on her own, because of the worsening of meteorism, to increase trimebutine to 450 mg TID a week earlier. Discontinuation of trimebutine, after VT interruption, achieved normalisation of QTc which was 420 ± 10 ms, a highly significant ($p<0.001$) difference (Fig. **3**). Signal averaging tests were not performed.

DISCUSSION

The actions of trimebutine [3,4,5-trimethoxybenzoic acid 2-(dimethylamino)-2-phenylbutylester] on the gastrointestinal tract are mediated *via* (a) an agonist effect on peripheral μ-, k- and δ- opiate receptors and (b) release of gastrointestinal peptides such as motilin and modulation of the release of other peptides, including vasoactive intestinal peptide, gastrin and glucagon. Trimebutine accelerates gastric

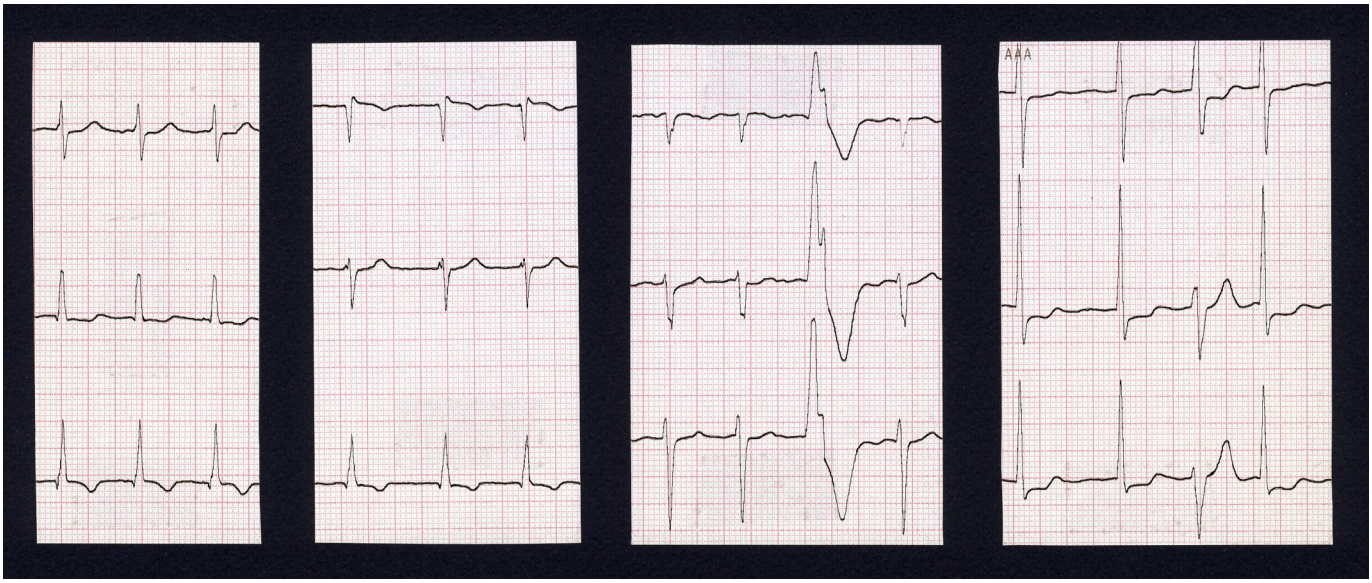

Fig. (3). Two days after admittance and trimebutine interruption another ECG showed persistent atrial fibrillation, premature ventricular beats and normalization of QTc (424 ms) always obtained by Bazett's [2] formula (average QT = 360 ms; average RR = 720 ms). When average QTc, measured using several complexes in this post-discontinuing trimebutine ECG (QTc = 420 ± 10 ms) was compared with that of Fig. (**2**), statistically significant shortening was concluded ($p<0.001$).

emptying, induces premature phase III of the migrating motor complex in the intestine and modulates the contractile activity of the colon. Clinically, trimebutine has proved to be effective in the treatment of both acute and chronic abdominal pain in patients with functional bowel disorders, especially irritable bowel syndrome, at doses ranging from 300 to 600 mg/day. It is also effective in children presenting with abdominal pain [19]. However, few electrophysiological investigations were carried out with trimebutine [17, 18, 20].

Cisapride (maleate) is an orally administered prokinetic agent used in the treatment of dyspepsia, diabetic gastroparesis, and gastroesophageal reflux disease, similarly to trimebutine or itopride hydrochloride. Although cisapride is useful and generally well tolerated, QT interval prolongation, TdP and sudden death have been reported in several cases [13-15]. Cisapride-induced arrhythmias are mediated by excessive prolongation of APD caused by blockade of I(Kr), leading to early afterdepolarization and TdP, but it is possible that pharmacokinetic mechanisms attributed to increased cisapride blood concentrations secondary to inhibition of cytochrome 450 3A4 metabolism by concomitant drug use of clarithromycin [14, 16], may contribute in clinics. Concomitant pharmacodynamic mechanisms related to additional blockade of cardiac potassium currents due to other drugs, disease states and electrolyte disturbances [3, 13] may cooperate. However, such interactions may reasonably be discounted in our patient.

The typical proarrhythmic response of antiarrhythmic drugs, particularly class III agents, but also of several non-cardiac agents, is TdP which can develop in normal hearts but is more likely to occur in hypertrophied hearts, higher drug doses or tissue concentrations, female-gender, hypokalemia, hypomagnesemia and bradycardia with concomitant greater QT prolongation [1, 3, 7]. However, among 190 patients who presented nontraumatic VT out-of-hospital cardiac arrest with a supraventricular perfusing rhythm and a measurable QT interval, 62% had monomorphic VT, whereas 38% had polymorphic VT of whom 49% (19% of total) presented with prolonged QTc and TdP [8]. Interestingly, patients with prolonged QTc were not more likely to have polymorphic VT [8]. On the other hand, monomorphic VT and prolonged QTc has long been associated with agents otherwise known to increase the risk of TdP, such as clarithromicin [9], cesium chloride [10] and dofetilide [11]. These cases demonstrate that astute clinicians must be alert to the appearance of proarrhythmia with a variety of agents if the electrophysiological milieu is altered alongside of the possibility that an atypical presentation may coexist with monomorphic rather than polymorphic (TdP) VT [11]. Of note, our patient had no ventricular hypertrophy.

Different drugs (digoxin, diuretics and acenocumarol) taken by our patient might have contributed, yet this appears unlikely, to increase trimebutine toxicity (represented by QT prolongation and monomorphic VT). Although creatine clearance was normal in our patient, mitral valve disease with AF might have had a role. It has been proposed, reporting dofetilide-induced monomorphic VT in a 41-year-old male about a decade postmitral valve replacement for rheumatic disease, with pre-drug normal QTc and AF, that the proarrhythmia mechanism might have been a drug-induced prolongation of refractoriness locally in diseased ventricular tissue, that could have impaired conduction such that the resulting inhomegeneity of repolarization and/or myocardial conduction produced a substrate for reentry [11]. Nevertheless, all this remains in the speculation domain and it is far from clear whether this could apply to explain proarrhythmia in our case.

A toxic effect of trimebutine seems crucial here. Indeed, the autonomous drug regimen (1.350 mg/day, the double of maximal recommended doses [19]) increase a week before emergency admittance and the normalisation of QT interval

at drug discontinuation (from 523 ± 12 to 420 ± 10 ms, $p<0.001$, compare Figs. **2** and **3**), constitute a strong argument since the close relationship among these events makes them improbable as simple coincidences. Therefore, although there is a lack of causative relation among trimebutine increased regimen, QT prolongation and monomorphic VT in our patient, who had an otherwise not completely normal heart, but normal hemodynamics and normal coronary arteries, yet presented with AF, we call attention to such an atypical presentation of drug-related proarrhythmia [11], probably due to toxicity. Whether this is due to an effect on both I(Kr) and I(Ks), as reported in guinea-pig ventricular tissue [18], deserves further investigation. Human myocardial tissues [2] may be appropriate for these studies, preferably concentration- and frequency-related.

It is also important to consider that in the rabbit, trimebutine exerts a Ca^{++} channel blocking effect on the sinus node pacemaker cells, since above 10 μmol/L produced a negative chronotropic effect accompanied by decreases in V_{max}, slope of phase 4 depolarization and APA. The effects on the current systems were depression of the slow inward current and a decrease in the current oscillations induced by elevating external calcium [17]. On the other hand, in the guinea pig isolated papillary muscles, trimebutine maleate showed a depressant action on the electrical activities of the fast- and slow-response fibres of the heart, mainly due to inhibitions of both fast Na^+ and slow Ca^{++} channels, since, always above 10 μmol/L, decreased V_{max} and APD_{90}, whereas the resting potential was not significantly altered. Trimebutine also depressed the slow action potentials of papillary muscles produced by 27 mmol/L K^+ and 0.2 mmol/L Ba^{++}. Finally, in spontaneously beating sino-atrial node preparations, trimebutine (above 10 μmol/L) decreased the heart rate, Vmax and the rate of diastolic depolarization [20]. The effect of trimbutine on heart rate might cooperate to increase QTc in man. However, our patient had AF, although average heart rate was slower while on trimebutine (Fig. **2**: RR = 840 ms) as compared to the ECG at discontinuation (Fig. **3**: RR = 720 ms). With the difficulties of measuring and correcting QT in presence of AF, these point need be further considered and elucidated in future research.

Proarrhythmia is the adverse effect that most frequently causes the withdrawal of drugs marketed either as antiarrhythmics or for other uses [1-3]. This reflects the uncertainty of preclinical studies in detecting this risk, mainly mediated by the ability to block potassium channels. In clinical practice it can be quite difficult to establish a definitive diagnosis of proarrhythmia in a particular patient. In the case of non-antiarrhythmic drugs causal association is established when an effect on cardiac ion currents, primarily potassium currents, is shown at experimental level, with the contribution to clinical QT elongation that, in most cases, leads to pause-dependent polymorphic tachycardia on predisposed people with a prior shorter QT interval. Although this case meets only some of the features mentioned above, and the causal association between the occurrence of arrhythmia and the use of high doses of trimebutine is only probable, the absence of prior similar descriptions makes it of interest, which may prompt recognition of further cases. Electrophysiological studies might help clarifying these cases and might become indicated whenever other cases are reported. To clarify the effects of trimebutine on heart rate and QT in man, it might be of importance to have ECG measured before, during and after drug regimen in the gastroenterological milieu. Due to well-known longer average QT in women, sex- specific grouping is warranted.

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