Ventricular Proarrhythmias Induced by Antiarrhythmic Drugs, Non-Cardiovascular Agents, and Implantable Antiarrhythmia Devices

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Summary

The authors briefly survey the electrophysiological mechanism and clinical spectrum of the aggravation of ventricular arrhythmias provoked by antiarrhythmic drugs, non-cardiovascular agents, and implantable cardioverter-defibrillators. The main aspects of the recognition, the differential diagnosis, and the treatments are discussed. It is emphasized that prevention of drug-induced arrhythmogenesis necessitates a fundamental understanding of the risk factors of proarrhythmias and of the clinical pharmacological properties of the drugs that are intended to be used, including proarrhythmic drug interactions. An account is presented of those drugs prescribed in non-arrhythmic states which may lead to ventricular fibrillation / ventricular tachycardia and out-of-hospital cardiac arrest. The proarrhythmic phenomena that may be observed in recipients of implantable cardioverter-defibrillators are discussed, as are the undesirable interactions between devices and antiarrhythmic drugs in such patients.

Key Words

Ventricular proarrhythmias, antiarrhythmics, non-antiarrhythmic drugs, implantable cardioverter-defibrillator

Introduction

Unfortunately, the vast majority of antiarrhythmic drugs (AADs) aggravate heart rhythm disturbances (in 3 – 15 % of cases); this phenomenon is known as proarrhythmia, or drug-induced arrhythmogenesis [1]. It occurs most often when an AAD increases the frequency and/or duration of the tachyarrhythmic episodes it is intended to suppress, but the AAD may also induce a life-threatening ventricular arrhythmia (VT/VF) by activating a previously dormant arrhythmic substrate, or by creating a de novo arrhythmogenic mechanism [2]. In recent years, those non-cardiovascular drugs capable of inducing ventricular tachyarrhythmias and sudden arrhythmic cardiac death (SACD) even in subjects with a structurally intact heart [3,4] have become of increasing interest to us. We also refer to a "proarrhythmic effect" if deterioration of a tachyarrhythmia is induced by an implantable antiarrhythmia device (pacemaker, ICD), either alone or in conjunction with an AAD [5,6].

Antiarrhythmic and Non-cardiovascular Drugs

At the present time, specifically characterized proarrhythmia syndromes can be distinguished from the underlying mechanisms, the clinical features, and the necessary therapeutic measures [1]. The proarrhythmic effect of AADs of the Vaughan Williams-Harrison Class I, which exclusively block (I/B) or predominantly block (I/C) the sarcolemmal sodium channels (I_{Na}), can be attributed to the use-dependent slowing of impulse conduction and facilitation of reentry [7]. The proarrhythmic potential of these drugs is usually manifested in the form of incessant or sustained monomorphic ventricular tachycardia (SMVT), accompanied by

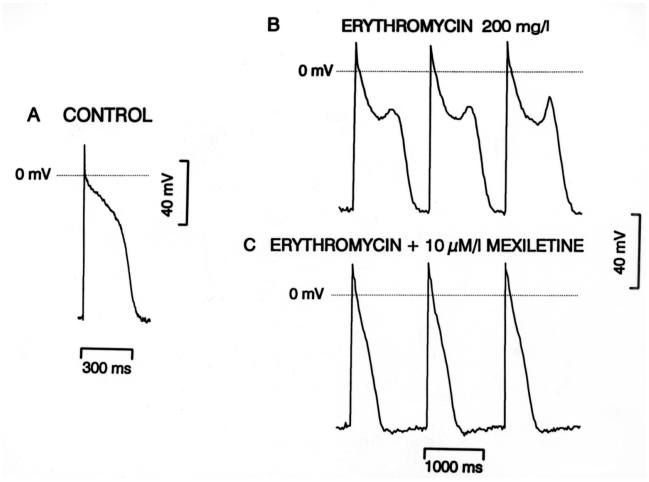

Figure 1. Transmembrane action potentials recorded from canine Purkinje fibers by the conventional microelectrode technique. Erythromycin (200 mg/l) induced early afterdepolarizations (EADs) at an average stimulation cycle length of 2344 ± 310 ms in all experiments (n = 9). The addition of mexiletine (10 mmol/l) markedly shortened the duration of the action potential, and the abolition of EADs was observed [12].

a wide QRS complex [2]. The use-dependent blockade of the fast Na^+-channels (I_{Na}) may be responsible for the clinical observation, that VT occurring in the presence of I/C AADs (flecainide, propafenone, moricizine) often commences in response to sinus tachycardia, e.g., exercise stress test [2]. The view is now widely accepted that, in post-MI patients, the additive negative dromotropic effect of acute ischemia and Na^+-channel blockers is responsible for the reentry-facilitation and the increased mortality observed in the course of randomized, controlled trials (RCTs), e.g., CAST I – II [8]. With regard to the generally slow VT induced by Na^+-channel-blocking AADs, the most important therapy is to withdraw the drug, but additional possibilities include overdrive suppression and (if there is not a volume overload) the intravenous administration of $NaHCO_3$ or Na-lactate [1].

The Class I/A and Class III AADs, which block cardiac potassium channels, and which lengthen the duration of action potentials (APD) and the QT interval, generally induce bradycardia/pause-dependent polymorphic VT (torsades de pointes) [4,9]. This arrhythmia is initiated by early afterdepolarizations (EAD) arising in the Purkinje cells with inherently long APDs, and is maintained by transmural reentry that can be ascribed to the presence of the mid-myocardial M-cell layer and to the reverse use-dependent increase in the dispersion of refractoriness [10]. In addition to removing the drug, therapy usually consists in intravenous administration of potassium and magnesium, and/or temporary transvenous pacing at a rate > 80 – 90 beats/min [11], but other APD-shortening drugs may also be effective, e.g., the slowly inactivating Na^+-current-blocking mexiletine (Figure 1) [12], or the ATP-dependent potassium channel opener nicorandil [9]. It has been experimentally demonstrated that certain AADs, which inhibit the rapidly activating delayed rectifier potassium current (I_{Kr}) with high potency, and the slow L-type Ca^{2+}-current ($I_{Ca\text{-}L}$) with somewhat lower potency (e.g., H 342/52 or BRL-32872), are capable of prolonging APD without provoking either EADs or torsades de pointes VT [13]. On the other hand, those I_K-blocking compounds that prolong phase 2 (plateau) repolarization without APD triangulation, instability, and reverse use-dependence, exert a significant antiarrhythmic effect without "torsadogenic" activity [14]. It is noteworthy that the specific (dofetilide, almokalant) and non-selective (quinidine, sotalol, ibutilide) blockers of I_{Kr} that is mainly responsible for the terminal (phase 3) repolarization are able to induce not only torsades de pointes, but also monomorphic VT (Figures 2 and 3) [15]; the ECG morphology of the ventricular arrhythmia is therefore of limited diagnostic value. Of the AADs that are currently used, oral amiodarone (with Class I/B and II and III and IV properties) has the lowest (< 2 %) proarrhythmic activity and can be administered safely even in patients with CHF [16]. It is almost certain that not even a combined I_{Kr} and I_{Ks}-block (azimilide, GLG-V-13, bepridil, indapamide, mibefradil) per se abolishes "torsadogenic" side-effects of AADs [9,17,18]. The longest-known, drug-acquired arrhythmia is ventricular bigeminy and monomorphic or bidirectional VT induced by digitalis glycosides, which can be attributed to tachycardia-dependent delayed afterdepolarizations (DAD) due to sarcoplasmatic reticular Ca^{2+}-overload [1]. The proarrhythmic activity of β-receptor blockers and heart rate lowering Ca^{2+}-antagonists (verapamil, diltiazem, gallopamil) is based on depression of sinoatrial (SA) impulse formation and atrioventricular (AV) conduction, and accordingly it appears in the form of sinus arrest, pronounced bradycardia or advanced AV block [1].

The CAST studies have clearly revealed that, if an anatomical substrate (e.g., post-MI scar) is present,

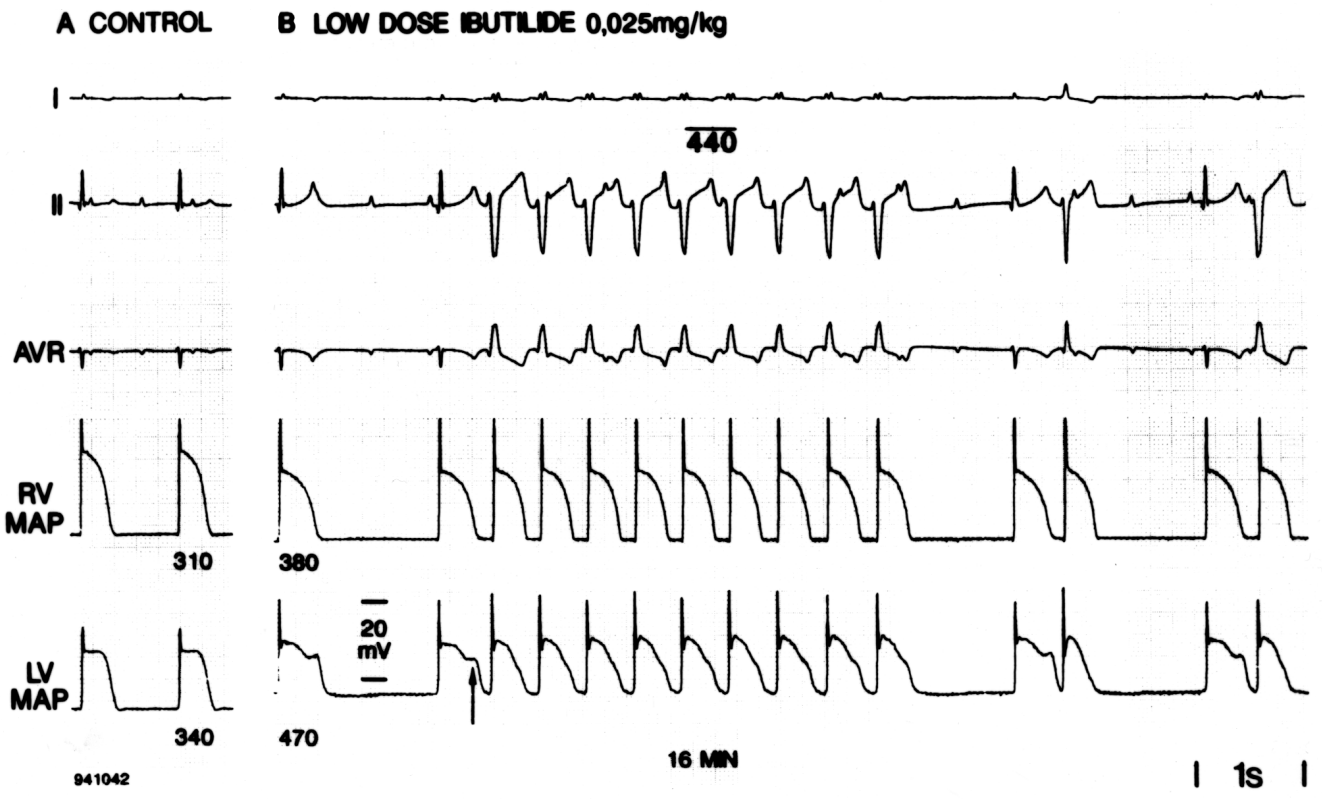

Figure 2. Ibutilide (0.025 mg per kg body weight)-induced non-sustained monomorphic ventricular tachycardia in a dog with chronic complete AV block. ECG limb leads (I, II, aVR) and intracardiac monophasic action potentials were recorded by the electrode-catheter technique from the right (RV-MAP) and left ventricle (LV-MAP). LV-MAP shows EAD-formation (indicated by an arrow) [15].

life-threatening, AAD-related ventricular tachyarrhythmias can occur not only in the first few weeks of pharmacotherapy (early proarrhythmia), but also much later (late proarrhythmia) [8]. Interim modification of the CAST-II protocol (allowing inclusion of post-MI patients with an LVEF of less than 40 %) shed light on the fact that one of the most important factors predisposing a patient to proarrhythmia is impaired systolic left ventricular function [8]. As regards the torsades de pointes VT developing on the basis of a lengthened ventricular repolarization, the most significant risk factors are hypopotassemia/hypomagnesiemia, bradycardia, female gender, prolonged (> 460 ms) pretherapeutic QT_c interval, and the interactive presence of another drug which lengthens the QT interval [4,9]. It is tempting to speculate that the decrease in the risk of SACD observed in some subgroups of large-scale CHF-RCTs (RALES, SOLVD) may be attributed to the "anti-torsades" action of the potassium-saving diuretic agent aldactone. The d-sotalol sensitivity of the ventricular myocardium is likewise enhanced by cardiac hypertrophy and electrical remodeling accompanied by downregulation of potassium channels (I_K, I_{to}) and by a prolongation of ventricular APDs [10]. Accordingly, certain authors currently consider biventricular hypertrophy to be a potential risk factor for drug-acquired torsades de pointes VT/VF.

In November 2000, Woosley and Franz established the International Registry of Drug-Induced Arrhythmias (ULR: http://www.qtdrugs.org), an electronic forum to universally register drug-induced arrhythmias and uniformly process the clinical data. This includes case reports provoked by AADs and non-CV drugs which lengthen QT. Although these drugs are prescribed for non-arrhythmic conditions, even in a therapeutic dose they display a considerable selective I_{Kr} (HERG)-blocking activity [3,4]. They include certain macrolides (erythromycin, clarithromycin, spiramycine) and

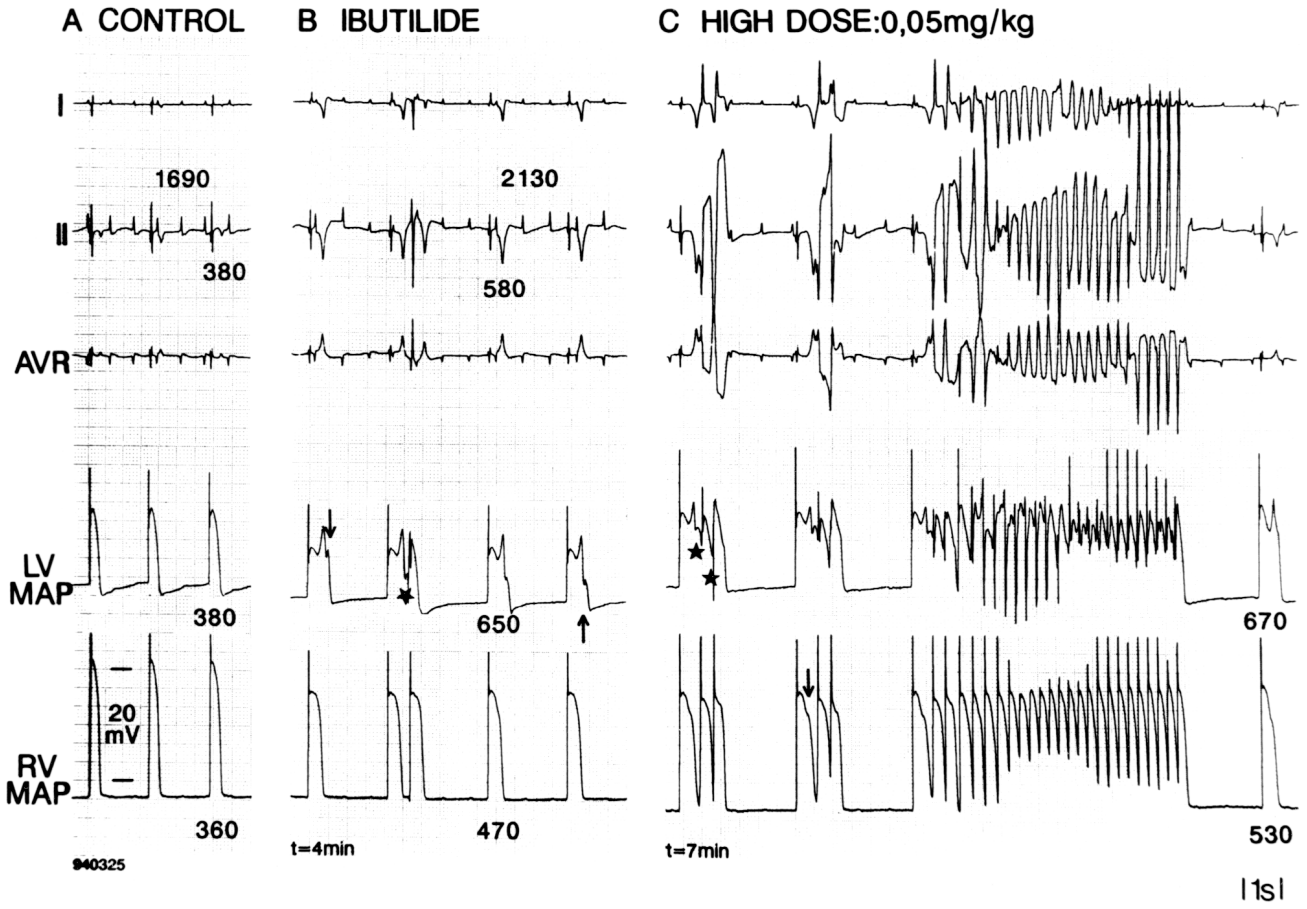

Figure 3. Ibutilide-induced (0.05 mg per kg body weight) non-sustained torsades de pointes ventricular tachycardia in a dog with chronic complete AV block. ECG limb leads (I, II, aVR) and intracardiac monophasic action potentials recorded by the electrode-catheter technique from the right (RV-MAP) and left ventricle (LV-MAP). Early afterdepolarizations (EAD) and EAD-induced ventricular extrasystoles are marked with arrows and asterisks [15].

fluoroquinolone antibiotics (sparfloxacin, grepafloxacin), some antimalarial agents (chloroquine, halofantrine), 2nd generation non-sedating antihistamines (astemizole, terfenadine, loratadine), certain gastrointestinal (GI) prokinetics (cisapride, domperidone), triazole-skeleton antimycotics (ketokonazole, flukonazole, itrakonazole) and a significant number of psychotropic drugs (phenothiazines, butyrophenons, tri- and tetracyclic antidepressants, pimozide, Li, chloralhydrate) [2,4,9]. Similar to cocaine, various tricyclic antidepressants (TCAs), e.g., imipramine or amitriptyline, block not only I_{Kr}, but also I_{Na}. Based on this information, it is readily understandable why a TCA overdose causes torsades de pointes VT in one patient and monomorphic VT with a broad QRS complex in another patient. Under in vitro conditions, sildenafil and domperidone display concentration-dependent inhibition of the I_{Kr} [19,20]. Therefore, the possibility exists that sooner or later case reports will announce that, in the presence of some predisposing factor, these drugs induce torsades de pointes VT and/or SACD. Recently, in a female patient with advanced structural heart disease (CHD and severe mitral valve prolapse), we observed the QT_c-interval-prolonging and profibrillatory effects of vinpocetine, a vasodilator that is widely utilized to treat diseases involving chronic cerebral hypoperfusion [21]. It has long been known that rapid intravenous injection of vinpocetine can provoke life-threatening ventricular arrhythmias (VT/VF), but in our case VF developed just after the administration of a slow drip infusion (40 mg vinpocetine dissolved in 500 ml physiological saline infusion); this indicates

that, in the presence of an enhanced susceptibility to arrhythmia, VT/VF may occur even when this cautious mode of administration is employed [21].

Implantable Cardioverter-Defibrillators

The results of RCTs have led to ICDs becoming the treatment of choice for patients at high risk of developing life-threatening ventricular tachyarrhythmias (sustained VT/VF) [22]. Theoretically, ICDs are capable of terminating not only native VT/VF (that is not suppressed by the AAD), but also drug-induced arrhythmia [6,23]. Additionally, even modern devices may give rise to aggravation of VT, which (though rarely) can increase morbidity associated with ICD therapy [5]. The causes of ICD-induced proarrhythmia include the following: suboptimal programming, a device malfunction (algorithm error, oversensing, mechanical malfunction), a drug-device interaction of a proarrhythmic nature, and external electromagnetic interference [5,22]. However, in all probability, there are also patients in whom the background involves the detrimental influence of autonomic modulating factors and the change of an arrhythmia substrate. A long-known complication of treatment of SMVT with antitachycardia (overdrive) pacing (ATP) is acceleration of the VT and its degeneration into VF [5,22]. In some cases, the (non-synchronized) shock provided by ICDs may precipitate atrial fibrillation (AFib) or atrial flutter; in the case of a rapid ventricular response, the device may react to this with a second, inappropriate shock. The ICD may also provide inappropriate antitachycardia therapy (possibly provoking rapid VT/VF) because it is unable to distinguish the native SVT or AFib from the VT [5]. Since AFib and other supraventricular tachyarrhythmias are relatively frequent in ICD recipients, the latest-generation dual-chamber (AV) devices provide treatment for these arrhythmias too [24]. The rare cause of inappropriate antitachycardia therapy may also be the oversensing of physiologic, non-QRS signals [22]. Asynchronous ventricular pacing with the aim of preventing post-defibrillation bradyarrhythmias may similarly be proarrhythmic [5]. Forty to seventy percent of ICD recipients also receive antiarrhythmic pharmacotherapy with the intention of preventing the recurrent device discharges and/or the supraventricular tachyarrhythmias, and in some of these cases there may be a proarrhythmic device-drug interaction [6]. The concomitant use of ICDs and AADs may cause increases in the defibrillation threshold (DFT) and in the VT cycle length below the detection cut-off rate [6,22]. In general, Na^+-channel blocker AADs (such as lidocaine or mexiletine) tend to raise the DFT, whereas drugs that block repolarizing potassium currents (such as sotalol, dofetilide or ibutilide) lower it [22,25]. Advances in ICD technology have reduced the importance of adverse drug effects. Nonetheless, one agent, chronic oral amiodarone, still demands special attention, for it could raise DFT to a clinically relevant degree [22]. The I/C AADs could increase pacing thresholds at rapid stimulation rates, leading to loss of capturing [22]. The same substances may cause a marked use-dependent QRS widening at elevated heart rates, and this may lead to rhythm misclassification and inappropriate shocks in patients whose ICDs use electrogram width or electrogram template enhancements. A stand-alone implantable atrial defibrillator (Metrix System, InControl, USA) does not induce ventricular arrhythmia; nevertheless, its production has been suspended: the development of sophisticated, multifunction, dual-chamber devices is increasingly coming into the limelight, as they are suitable for the treatment of atrial and ventricular tachyarrhythmias and bradyarrhythmias alike [22,24]. Further clinical observations are clearly necessary in order to establish, whether these latest-generation ICDs have a proarrhythmic potential.

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