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Drug-induced QRS morphology and duration changes

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Abstract

Drug-induced ECG changes may affect all components of the ECG curve. The attention of regulatory agencies, researchers and clinicians has been directed towards drug-induced QT-interval prolongation and its well-documented proarrhythmia. This presentation focuses on drug-induced changes, i.e., morphology, amplitude and QRS complex duration (QRSd). A great variety of pharmacological agents (e.g., class IA and IC antiarrhythmics, antihistamines, antidepressants, antipsychotics) exert an influence on the QRSd. The QRSd is assessed by a variety of ECG methodologies. Standardization of measurements of QRSd ensures the comparability of results by different ECG modalities, and of serial QRSd assessments. Some analgesics and hypoglycemic agents influence the amplitude of QRS complexes by way of their propensity to cause peripheral oedema (extracardiac mechanism). Perhaps a new culture could evolve in which the entire ECG curve, from the onset of the P-wave to the offset of the U-wave, will be used in the evaluation and monitoring of drug safety, with emphasis primarily on the standard ECG. (Cardiol J 2008; 15: 505–509)

Key words: ECG, QRS duration, drug-induced ECG changes, drug-induced QRS duration changes, drug-induced QRS morphology changes, drug-induced QRS amplitude changes

Introduction

In this presentation, remarks will be limited to drug-induced changes in QRS duration (QRSd), morphology and amplitude. Prolongation of the QT--interval (QT) has been primarily emphasized by regulatory agencies, pharmaceutical industry, researchers and clinicians, due to its documented association with proarrhythmia [1]. The role of changes in the QRSd, morphology and amplitude in the evaluation and monitoring of drugs is discussed, and some comments about measuring the QRSd are presented.

Prolongation of QRS duration

The QRSd reflects the duration of ventricular depolarization, and its measurement differentiates normal intraventricular conduction (< 100 ms) from bundle branch blocks (BBB) and intraventricular conduction delays (IVCD) [2]. Depolarization of atrial and ventricular myocytes depends mainly on the fast response inward Na^+ current, which determines the slope of phase 0 and the amplitude of action potentials. Blockade of the Na^+ current leads to attenuation of the rate and magnitude of depolarization, which in turn slows the transmission

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of action potentials among myocytes, with a resultant decrease in the velocity of the excitation conduction, and prolongation of the QRSd. This slow spreading of depolarization underlies the suppression or interruption of proarrhythmic re-entry, but could also result in incessant ventricular arrhythmias (VA). Many antiarrhythmic drugs exert an effect by blocking the Na^+ current, and some prolongation of QRSd is an indicator of their desired pharmacologic effect. The question is whether prolongation of the QRSd is indicative of proarrhythmia to the same degree as it is in the case in QT prolongation, and thus could be employed in drug monitoring independently of associated QT. Some non-antiarrhythmic cardiac and noncardiac drugs also block the Na^+ current and thus prolong the QRSd; for such agents these effects are considered adverse responses of their pharmacodynamic profile, particularly when they lead to VA. In general, prolongation of the QRSd is less frequent than prolongation of the QT, although occasionally one of these 2 ECG parameters can be prolonged at the exclusion of the other. Usually, the standard ECG (ECG) is less sensitive than the signal-averaged ECG (SAECG) in documenting prolongation of the QRSd.

Class I drugs (Na^+ current blockers) of the Vaughan-Williams antiarrhythmics classification prolong the QRSd with the agents of subclasses IC, IA, and IB, producing this effect in a descending order of magnitude, based on the intensity of the Na^+ channel blockade they induce. With the exception of type IB drugs (lidocaine, tocainide, mexiletine, phenytoin), all class I drugs result in significant QRSd prolongation. Type IC drugs (flecainide, propafenone, moricizine) lead to larger changes in the SAECG QRSd prolongation than IA (quinidine, procainamide, disopyramide) or IB, and the combination of IA and IB drugs. These changes in the SAECG reflect prolongation of the initial portion of the QRS complex and late potentials, i.e., they induce a global slowing of ventricular activation. Procainamide, a class IA agent, prolongs the SAECG QRSd in patients with inducible VA, with a $> 15\%$ prolongation being the best parameter that identifies effectively treated patients [3]; in other studies of class I antiarrhythmic drugs, SAECG QRSd prolongation failed to predict drug efficacy, although these drug-induced changes may be helpful in categorizing antiarrhythmic agents [4, 5]. Changes in the serum concentration of class I agents and SAECG QRSd correlated well in patients receiving chronic care, thus rendering repeat blood drug concentration measurements unnecessary [6]. Class IA agents also have a K^+ channel blocking effect, which is responsible for the prolongation of the effective refractory period (ERF) induced by these drugs. Class IC drugs, flecainide and pilsicainide prolong the SAECG QRSd. Class III (K^+ channel blockers responsible for phase 3 of repolarization) drugs also prolong the QRSd, since they also possess some Na^+ blocking effect. Many class III drugs have mechanisms of action that are shared with drugs found in the other classes. For example, amiodarone, a Class III antiarrhythmic, also exerts Na^+ and Ca^{++} channel blocking actions. Class III antiarrhythmic agents (amiodarone, bretylium, sotalol, dofetilide, ibutilide) block the K^+ channel repolarizing currents and prolong the action potentials and the ERP. Amiodarone prolonged the SAECG QRSd in patients with old myocardial infarction, who underwent programmed ventricular stimulation, and such changes were more pronounced in patients with no inducible VA, while the ECG was not sensitive in detecting amiodarone induced QRSd prolongation [7]. However, dofetilide (a pure Class III antiarrhythmic agent) did not change the SAECG, and no SAECG parameter predicted the results of programmed ventricular stimulation [3]. Azimilide, a class III antiarrhythmic agent, increased the action potential duration, QT, and ERP, but did not affect the QRSd [8].

Noncardiac drugs also have an effect on the QRSd. The histamine H1 receptor antagonist astemizole markedly depresses the rate of rise of the action potential (Vmax) and prolongs the QRSd, with terfenadine showing smaller such effects. The effect of different histamine H1 receptor antagonists on the ERP, and thus on QT, is variable. Overdose with dextropropoxyphene, an opioid which is used in combination with the analgesic acetaminophen, and is a cause of hospital admissions and death in Australia and the UK, leads to a dose-dependent prolongation of the QRSd, but no changes in the QT [9]. Coadministration of some of these drugs with the antifungal itraconazole, or other cytochrome P450 3A4 inhibitors, intensifies their effects on the QRSd [10]. The "prokinetic" drug cisapride did not have an effect on the QRSd while it prolonged the QT [11]. Amitriptyline in combination with a benzodiazepine was the most common antidepressant taken by patients, and led to a prolonged QRSd and QT, but no arrhythmias were observed in patients with an overdose [12]. The tricyclic antidepressants dosulepin and amitriptyline may cause fatal poisoning and prolong both the QRSd and QT [13]. The antidepressant maprotiline prolongs the QRSd without causing arrhythmias [14]. Desipramine, an antidepressant, was associated with

prolongation of the QRSd and QT, although the correlation of drug levels and the ECG parameters was poor [15]. ECG changes with tricyclic antidepressant agents are attributable primarily to the Na^+ channel blockade caused by these agents. The majority of patients at significant risk of developing cardiac or neurological toxicity from these agents will have a QRSd > 100 ms, or a rightward shift of the terminal 40 ms of the frontal plane QRS complex vector [16]. Some antimalarial drugs delay ventricular depolarisation slightly (class IC effect), resulting in prolongation of the QRSd, and some have ventricular repolarisation (class III) effects. The anthracycline daunorubicin induces a significant and progressive prolongation of the QRSd. The ECG appears to be of limited value in the assessment of cardiac toxicity with Adriamycin therapy [17]. A large number of other drugs, tricyclic and teracyclic antidepressants, antipsychotics, and anticonvulsives prolong the QRSd via a blocking effect on cardiac Na^+ currents. Thus, the above listing of some drugs prolonging the QRSd is a small sample of what the literature comprises on this topic.

Measurement of QRS complex duration

Many ECG modalities have been employed in the measurement of the QRSd (the ECG, the SAECG, the Frank vectorcardiogram (VCG), the exercise ECG and the Holter ambulatory ECG). Measurements are carried out manually or executed by automation-based algorithms [2]. Single specific leads, groups of leads or the entire array of leads of the ECG are employed. Often, automated algorithms calculate a "global" QRSd, which is based on different leads, for each manufacturer of electrocardiographs. When the SAECG is employed, information about late potentials is referred to, along with the duration of the filtered total QRS complex. Manual measurements are made from hard copies, digitized ECGs or digital ECGs on the computer screens. Magnification is employed on the hard copies or the computer screens. Hand-held or electronic callipers are utilized. ECG recording at double or higher speed, at standard or double calibration, is occasionally used. Occasionally no mention is made in literature reports of the methods used to measure the QRSd. The definition of offset is less of a problem in the measurement of the QRSd than it is with the QT. Nevertheless, the definition of both the onset and offset is problematic since manual methods use a subjective estimate as to where these points belong. Automated algorithms rely either on computer algorithms using QRS derivatives or spatial vector velocity parameters [2, 18, 19]. A spectral method, based on the fact that the QRS complexes comprise significant frequencies greater than 50 Hz, used a 50–300 Hz digital filter and an SAECG to reduce in the noise and, to QRSd measurements [18, 19]; the results by this method had an excellent correlation with carefully made visual determinations of QRSd carried out in ECG recordings at high speed and gain. No work has been done on comparing methods such as the one described herein based on spectral content with others using the morphology or slope of QRS complexes. Since QRSd prolongation with drugs is often frequency dependent [20], comparisons of QRSd values, when drugs are evaluated, should take the heart rates into account. Casual observations of data from exercise ECGs or Holter ambulatory ECGs suggest a dynamic character of QRSd over time. Increasing QRSd with increasing heart rates is not unusual even in seemingly normal subjects, and thus the evaluation of changes in the QRSd should always be considered in conjunction with the corresponding heart rates.

Since studies evaluating drugs employ the ECG and/or the SAECG, it is important to evaluate how the different ECG modalities compare in reference to measurements of QRSd. Comparison of the QRSd measured by ECG, VCG and SAECG in patients with prior myocardial infarction, excluding patients with bundle branch block (BBB) [21], showed that the QRSd was the same by SAECG and VCG, but longer than the QRSd by ECG, in patients without spontaneous or inducible VA; QRSd was longer by SAECG than VCG, and the QRSd by the latter was longer than the QRSd by the ECG in patients with spontaneous or inducible VA; the QRSd was longer by all 3 modalities in patients with spontaneous VA than in patients without spontaneous or inducible VA; a QRSd on VCG ≥ 110 ms and on ECG ≥ 100 ms had a sensitivity of 93% and 77% and a specificity of 83% and 85%, respectively, for predicting an abnormal SAECG result, and thus measurements of QRDd from any of these 3 ECG modalities could detect the patients with myocardial infarction prone to VA. Extrapolation of the results of this study to the setting of drug evaluation or monitoring suggests that any of these 3 ECG methodologies can be used in serial QRSd measurements, providing that one keeps in mind that the QRSd is inherently shorter by ECG than by SAECG or VCG. Sources of variation in values of QRSd from serial ECG recordings in the same patients are: the inherent over-time variation of QRSd, the different leads used for its calculation by different proprietary

automated algorithms, and the failure to adhere to the recommended placement of precordial electrodes on the chest wall. Age- and gender-specific normal values have been published [2]. Exercise often increases QRSd, and some of these changes lead to morphology changes of the QRS complexes or to various degrees of BBB or IVCD. SAECG-based measurements of QRSd are considered more accurate and have been used extensively in research (vide supra). In addition, ambulatory ECG-based measurements of QRSd are occasionally used and this provides the advantage of a dynamic assessment of this parameter. These two latter technologies should not replace the standard ECG-based assessment of QRSd, which should be used routinely and repeatedly by all physicians in patients treated with drugs known to influence this measurement. There is some literature on QRS dispersion and QRS/QT dispersion [22]; however, these parameters have not found an application in drug research. Due to the much clearer inscription of the offset of QRS complexes, in contrast to QT-intervals, the problems in the measurement of QRSd are much smaller than those encountered with QT measurements. Consensus among manufacturers of electrocardiographs about the algorithm of the "global" QRSd calculation will provide comparability of values generated by different ECG machines. The value of changes in the QRS complexes, as predictors of drug-induced arrhythmogenicity, will be enhanced by studying frequently obtained ECGs in terms of QRSd and morphology and amplitude of the QRS complexes in both research and practice. The voluminous literature on drug-induced QT either does not include information on the QRS complex, or when it does, such information is not analyzed in a multivariate fashion in order to evaluate the independent proarrhythmic role of QRSd. Such scrutiny of the ECG should be done with pari passu observations of the corresponding QTs. Drug-induced increase in QRSd is probably less sensitive than increase in QT, but it may have an independent value in the evaluation of certain drugs.

A number of questions in reference to various drugs need to be settled: 1) Does the QRSd have any predictive value, independent of the QT? 2) Does the QRSd have an additive value when it is used in conjunction with the QTs? 3) At what percentage increase of QRSd should one have concerns about the continuation of drug(s) administered? 4) Does a change in the QRSd affect the corresponding QT, and thu can the J-T interval also be assessed in parallel with the QT? Indeed, it has been shown that an increase in QT could occasionally be accounted for primarily by the corresponding increase in the QRSd, without any change in the J-T in patients treated with IC and IA drugs [23]. Answers to some of these questions could probably emanate from the data of published studies on QTs and drug-induced proarrhythmia. Such a correlative approach in future studies and in practice may enhance our predicting power of detecting drug-induced proarrhythmia.

Changes in QRS amplitude

Intuitively, drugs blocking the Na^+ peak current and attenuating the velocity of phase 0 slope and the amplitude of action potentials are expected to cause a reduction of the amplitude of QRS complexes; however, no literature on this is available, particularly in reference to the ECG. There was a decrease in the voltage of the entire filtered QRS in SAECG with tricyclic antidepressants [24]. Nevertheless, a reduction in the QRS amplitude of the ECG has been noted with some drugs which have in common the development of peripheral oedema (PERED) as a side effect. It is important to note that such a reduction is *extracardiac* in mechanism due to the effect of the body volume conductor on the cardiac potentials as they are transferred to the body surface [25]. Rofecoxib, a nonsteroidal anti-inflammatory drug, which is a selective COX-2 inhibitor, may produce reversible PERED in association with reversible reduction of the amplitude of QRS complexes [26]. In addition, thiazolidinediones, the antidiabetic drugs, induce reversible PERED, which leads to attenuation of QRS complexes [27]. One can only speculate that such ECG manifestations are common with other drugs with a propensity of PERED as a side effect, and this deserves evaluation. Another matter that needs consideration is the changes in QRSd resulting from changes in the QRS amplitude. Such changes in the amplitude lead to a shortening of QRSd [28], probably due to the failure to include in the QRSd the measurement of a portion of the onset and offset of the QRS complexes, which, by attenuation of the QRS amplitude, renders them indistinguishable from "noise". This speculation was confirmed in a study of artificial attenuation of the QRS amplitudes, which resulted in a shortening of the QRSd [29]. The above apply to patients with congestive heart failure or other oedematous states in which the possible drug-induced changes in the QRSd should be interpreted in the context of the associated attenuation/augmentation of the magnitude of the QRS complexes.

Changes in QRS morphology

There is no literature about drug-induced QRS morphology changes. However, one can speculate that changes in the velocity of depolarization can affect various myocardial regions in structurally normal or abnormal hearts in different ways. This might lead to changes in the absolute and relative amplitudes of R- and S-waves, in QRS notches, and in high frequency components of the ECG. There is a great deal of literature on drug-induced increases in late potentials, reflecting the amplitude/ /morphology of these high frequency late transients in the SAECG [3–7], but these changes do not pertain to the ECG. Changes in the QRS axis [13] may result in changes in the morphology of some of the ECG QRS complexes. A rightward shift of the terminal 40 ms frontal plane QRS vector has been described with tricyclic antidepressants [16], and this would entail changes in QRS complex morphology.

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