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Drugs and Brugada syndrome patients: review of the literature, recommendations and an up-to-date website (www.brugadadrugs.org)

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Abstract

Background: Worldwide, the Brugada syndrome has been recognized as an important cause of sudden cardiac death at a relatively young age. Importantly, many drugs have been reported to induce the characteristic Brugada syndrome-linked ECG abnormalities and/or (fatal) ventricular tachyarrhythmias.

Objective: To review the literature on the use of drugs in Brugada syndrome patients, to make recommendations based on the literature and expert opinion regarding drug safety, and to ensure worldwide online and up-to-date availability of this information to all physicians who treat Brugada syndrome patients.

Methods: We have performed an extensive review of the literature, formed an international expert panel to produce a consensus recommendation to each drug, and initiated a website (www.brugadadrugs.org).

Results: The literature search yielded 506 reports to be considered. Drugs were categorized to one of four categories: 1) drugs to be avoided (n=18), 2) drugs preferably avoided (n=23), 3) antiarrhythmic drugs (n=4) and 4) diagnostic drugs (n=4). Level of evidence for most associations

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was C (only consensus opinion of experts, case studies, or standard-of-care) as there are no randomized studies and few non-randomized studies in Brugada syndrome patients.

Conclusions: Many drugs have been associated with adverse events in Brugada syndrome patients. We have initiated a website (www.brugadadrugs.org) to ensure worldwide availability on safe drug use in Brugada syndrome patients.

Introduction

Worldwide, the Brugada syndrome (BrS) has been recognized as an important cause of sudden cardiac death at a relatively young age. BrS is diagnosed in the presence of specific electrocardiographic abnormalities (known as the type-1 BrS-ECG, figure 1) combined with an absence of gross structural abnormalities and several other criteria.[1,2] In addition, BrS often shows familial aggregation.

The presence of this type-1 BrS-ECG in particular has been linked to an increased risk for ventricular tachyarrhythmias, cardiac arrest and sudden death in BrS-patients.[3] Importantly, many drugs have been reported to induce the type-1 BrS-ECG and/or (fatal) arrhythmias in BrS-patients (figure 2). Therefore, patients with BrS should be advised not to use these drugs or to use them only under controlled conditions.

Although the most appropriate treatment in BrS is under discussion,[4,5] avoidance of potential proarrhythmic drugs and fever (a well-known trigger of cardiac events in Brugada syndrome)[6,7] are generally accepted to be an important part of (prophylactic) treatment. However, some patients may (only) be appropriately treated with an implantable cardioverter-defibrillator. In contrast, there are also drugs that may have antiarrhythmic effects and may thus be used favorably in the acute or chronic setting.[8–10] As BrS has a rather low prevalence (estimated at 1 in 2000, varying in different regions in the world),[1] these and other critical characteristics of BrS are certainly not common knowledge for many physicians.[11]

With the aim of aiding all physicians who treat patients with BrS, we discussed the interaction between drugs and BrS, performed an extensive review of the literature, formed an international expert panel to produce a consensus recommendation for each drug, and initiated a website (www.brugadadrugs.org, figure 3) to ensure world-wide online and up-to-date availability of this knowledge base.

Methods

Literature review

PubMed (Text: Brugada; MeSH Terms: Chemicals and Drugs Category; only reports in English were considered) and expert knowledge was employed to investigate drugs that have been associated with the type-1 BrS-ECG, with arrhythmias or with antiarrhythmic properties in BrS-patients. Although there is large variation in the extent to which different drugs have been associated with BrS, we aimed to investigate the first reported drug-BrS association for each drug, but favored larger, combined clinical-experimental or otherwise important studies (e.g., those that report arrhythmias). Thus, we refer to many, but not to all reports that describe a certain drug-BrS association. Furthermore, we sought drugs with cardiac ion channel blocking effects that, hypothetically, have the potential to have deleterious effects in BrS-patients, but that have not yet been reported deleterious effects. Finally, for most drugs with clinical association with BrS, we were able to retrieve confirmatory experimental studies showing the effects of the drug on the cardiac electrophysiology.

Recommendations

As there are no randomized clinical trials in BrS, the level of evidence (ACC/AHA/ESC format) for most associations is C (only consensus opinion of experts, case studies, or standard-of-care) and for some associations B (non-randomized studies). To ascertain validity of recommendations given, the authors formed an international expert panel (the 'BrugadaDrugs.org Advisory Board') to summarize the clinical and experimental evidence and expert opinion. The classification of recommendation is expressed in a modified ACC/AHA/ESC format:

- Class I: There is evidence and/or general agreement that a given treatment is potentially proarrhythmic (or potentially antiarrhythmic) in BrS-patients.
- Class IIa: There is conflicting evidence and/or divergence of opinion about the drug, but the weight of evidence/opinion is in favor of a potentially proarrhythmic (or potentially antiarrhythmic) effect in BrS-patients.
- Class IIb: There is conflicting evidence and/or divergence of opinion about the drug and the potential proarrhythmic (or potentially antiarrhythmic) effect in BrS-patients is less well established by evidence/opinion.
- Class III: There is very little evidence and/or agreement that a drug is potentially proarrhythmic (or potentially antiarrhythmic) in BrS-patients

Subsequently, we have listed the drugs into four groups:

- Drugs to be avoided by BrS-patients
- Drugs preferably avoided by BrS-patients
- Potential antiarrhythmic drugs in BrS-patients
- Diagnostic drugs in BrS

Within these groups, we differentiated between different drug classes (e.g., antiarrhythmic drugs and psychotropic drugs).

Results

The PubMed search yielded 563 reports, including 506 written in English. The BrugadaDrugs.org Advisory Board selected approximately 15% of these reports as adding considerably to our knowledge and understanding of drug effects in BrS. The drugs and accompanying recommendations are listed in Tables 1 through 4.

Discussion

In this study we reviewed the literature on the use of drugs in BrS-patients and made recommendations about their safety that were based on the literature and expert opinion. We also initiated a website (www.brugadadrugs.org) where these drugs and the recommendations can be accessed by all physicians who treat patients with BrS and by others with possible interest (e.g., patients). On this website, we provide more detailed information on drugs in BrS than reviewed in this manuscript. In addition, the website is updated frequently (drugs added or removed, recommendations changed) according to the latest evidence.

Patients with BrS should be advised not to take the drugs from the 'avoid' and 'preferably avoid' lists or to use these drugs only after extensive consideration and/or in controlled conditions. We advise patients to give a list of these drugs to all of their health care providers (including their general practitioner, dentist and pharmacist). In many BrS-

patients, avoidance of these drugs (and treatment of fever)[6,7] is probably an appropriate and safe treatment. Furthermore, some BrS-patients seem to perform well on quinidine.[8-10] Recently, a prospective registry has started investigating the use of empiric quinidine therapy for asymptomatic BrS-patients (ClinicalTrials.gov identifier NCT00789165).[12] Further, the QUIDAM study (Hydro**Qui**nidine to **D**ecrease **A**rrhythmic events in Brugada syndro**m**e patients, ClinicalTrials.gov identifier NCT00927732), a French national double blinded randomized study, is currently performed on the role of quinidine therapy to improve the outcome in high risk BrS-patients. Reports have postulated an antiarrhythmic effect of other drugs (amrinone,[13] bepridil,[14,15] clarithromycin,13 denopamine,[15] dimethyl lithospermate B,[16] mexiletine,[17,18] milrinone,[13] phentolamine,[17] prazosin,[17] sotalol,[19,20] tedisamil13,21 and 4-aminopyridine13). We consider the evidence on use of these drugs as antiarrhythmic treatment in Brugada syndrome patients currently to be too low.

An important issue regarding ventricular tachyarrhythmias in Brugada syndrome patients is that they can present as an epileptic seizure and that the cerebral hypoperfusion may create a clinical picture easily confused with a postictal phase. Therefore, in patients with seizures both epilepsy and arrhythmia syndromes such as Brugada syndrome7 (or, e.g., Long-QT syndrome)22 are part of the differential diagnosis. Many antiepileptic drugs, such as carbamazepine or phenytoin, act through cerebral ion channel blockade but will also result in cardiac ion channel blockade.[23-25] The latter may have a deleterious (and possibly fatal) effect in patients with an arrhythmia syndrome such as Brugada syndrome. Therefore, it is important to exclude arrhythmia syndromes such as Brugada syndrome in patients suspected of epilepsy before a possible harmful treatment is started.

We hope that the website will be of help to physicians who are in need of this information and we welcome your suggestions and/or documentation on the safe or unsafe use of drugs in BrS-patients. Further, we hope that the information on our website will prevent BrS-patients from suffering a cardiac arrest or sudden cardiac death initiated by drugs that should be avoided.

Limitations

The principal limitation of the association between certain drugs, BrS and arrhythmias, is the limited number of case reports and experimental studies suggesting an effect in BrS. Further, there may be conflicting results and large variability may exist between BrS-patients in their response to certain drugs. This response may also vary in different conditions (e.g., with or without fever, drug in therapeutic range, overdosed or in combination with other drugs etc.). Therefore, clinical decision making should be based on more than the presence or absence of a (single) association in another patient. Additionally, it remains important for health care providers to recognize the active substances in medicines containing a combination of drugs, and to be aware of the drug category (e.g., many tricyclic antidepressants will be potentially proarrhythmic in BrS-patients).

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The inspiration for the website comes from www.qtdrugs.org, which contains lists of drugs associated with the Long-QT syndrome.

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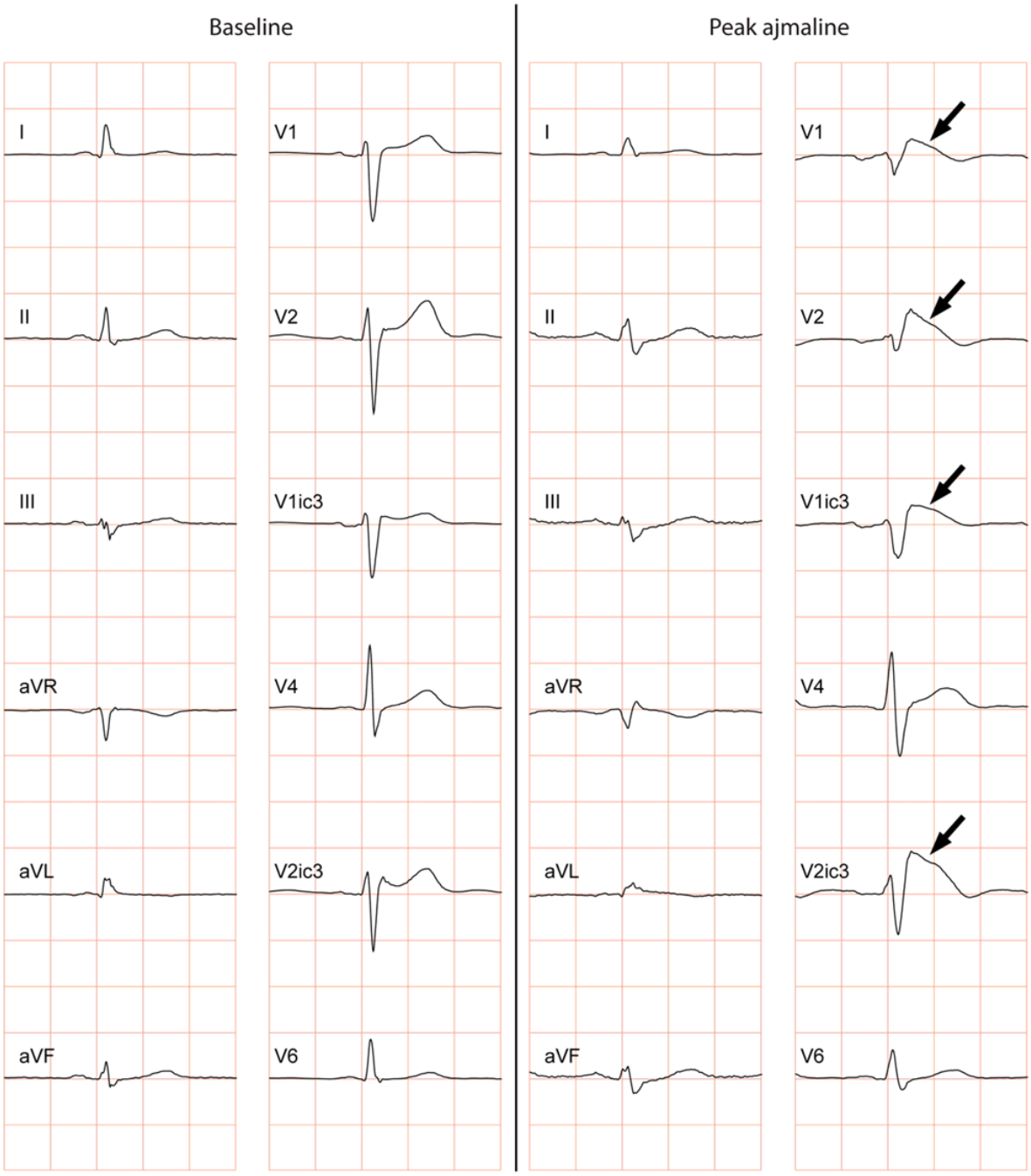

Figure 1.
Conversion of a normal ECG into a type-1 BrS-ECG during ajmaline challenge. Note the coved-type ST-segments (arrows) in the right precordial ECG leads at peak ajmaline (note V3 is placed in the 3rd intercostal space above V1 [V1ic3], and V5 is placed in the 3rd intercostal space above V2 [V2ic3]).

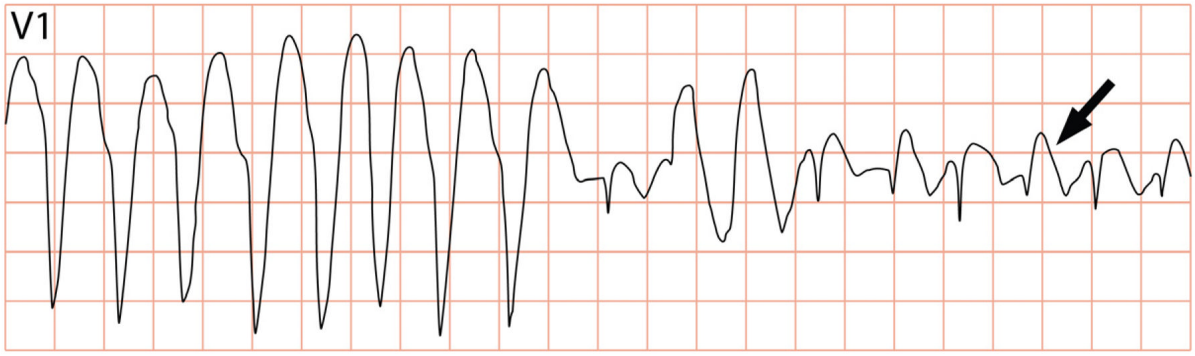

Figure 2.
Non-sustained ventricular tachycardia in a patient who was given flecainide for paroxysmal atrial fibrillation, note the coved-type ST-segments (arrow). The patient was diagnosed with BrS during an ajmaline provocation test.

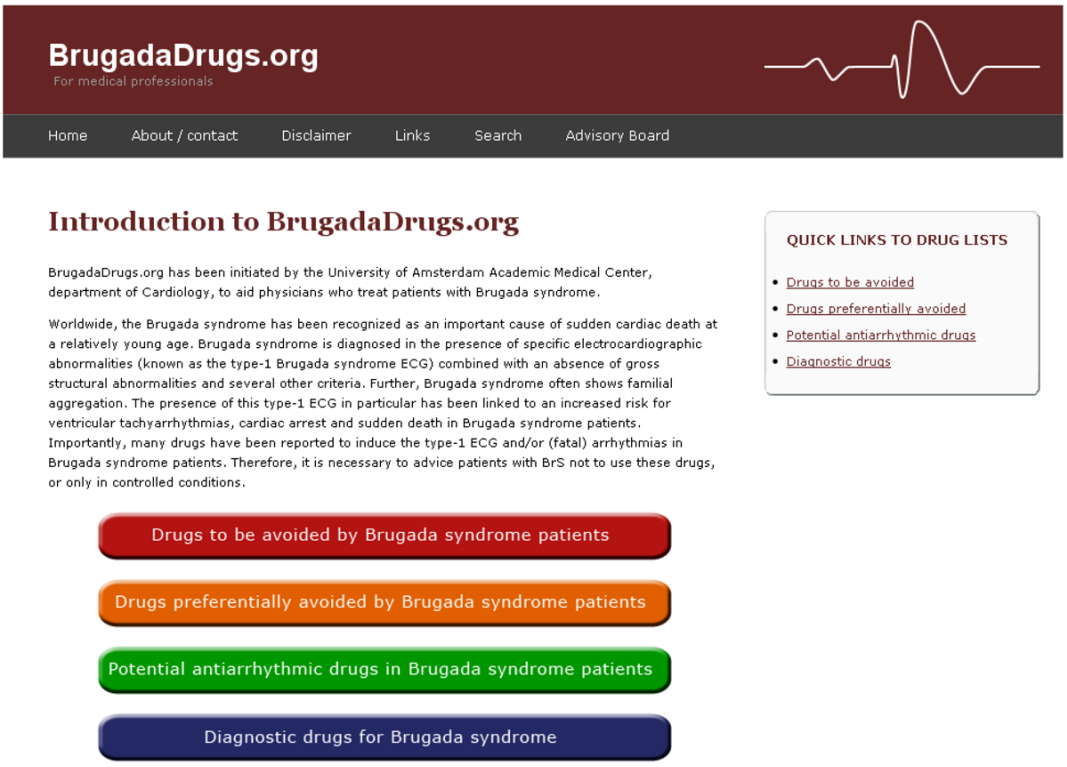

Figure 3.
Screenshot of the website at www.brugadadrugs.org

Table 1

Drugs to be avoided by Brugada syndrome patients

Drug category	Drug (generic)	Recommendation
Antiarrhythmic drugs:	Ajmaline[26-29]	Class I
	Flecainide[30-34]	Class I
	Pilsicainide[35-38]	Class I
	Procainamide[17,26,39,40]	Class I
	Propafenone[41-45]	Class IIa
Psychotropic drugs	Amitriptyline[46-49]	Class IIa
	Clomipramine[50,51]	Class IIa
	Desipramine[52-55]	Class IIa
	Lithium[52,56]	Class IIa
	Loxapine[47,57]	Class IIa
	Nortriptyline[55,58,59]	Class IIa
	Trifluoperazine[47,60]	Class IIa
Anesthetic drugs	Bupivacaine[61-64]	Class IIa
	Propofol[62,65-67]	Class IIb
Other substances	Acetylcholine[17,68,69]	Class IIa
	Alcohol (toxicity)[47,70,71]	Class IIb
	Cocaine[72-75]	Class IIa
	Ergonovine[68,76]	Class IIb

Recommendation: Class I: convincing evidence/opinion; Class IIa: evidence/opinion less clear; Class IIb: conflicting evidence/opinion.

Table 2

Drugs preferably avoided by Brugada syndrome patients

Drug category	Drug (generic)	Recommendation
Antiarrhythmic drugs:	Amiodarone[77-79]	Class IIb
	Cibenzoline[80-82]	Class IIb
	Disopyramide[14,17,83-85]	Class IIb
	Lidocaine[17,86*]	Class IIb
	Propranolol[17,18,70,87,88]	Class IIb
	Verapamil[17,89,90]	Class IIb
Psychotropic drugs	Carbamazepine[91,92]	Class IIb
	Cyamemazine[47,93]	Class IIb
	Doxepin[48,94]	Class IIb
	Fluoxetine[47,51]	Class IIb
	Imipramine[95]	Class IIb
	Maprotiline[46,96]	Class IIb
	Perphenazine[46,97]	Class IIb
	Phenytoin[98,99]	Class IIb
	Thioridazine[100]	Class IIb
Antianginal drugs	Diltiazem[1,101-103]	Class III
	Nicorandil[1,104]	Class III
	Nifedipine[1,105]	Class III
	Nitroglycerine[1,106,107]	Class III
	Sorbidnitrate[1,89,108]	Class III
Other substances	Dimenhydrinate[109-111]	Class IIb
	Edrophonium[17,18]	Class IIb
	Indapamide[112]	Class IIb

Recommendation: Class I: convincing evidence/opinion; Class IIa: evidence/opinion less clear; Class IIb: conflicting evidence/opinion; Class III: very little evidence.

* Note that lidocaine use for local anesthesia seems to be safe if the amount administered is low and if combined with adrenaline which results in a local effect only.

Table 3

Potential antiarrhythmic drugs in Brugada syndrome patients

Drug category	Drug (generic)	Recommendation
Antiarrhythmic drugs	Isoproterenol / Isoprenaline[15,17,113,114]*	Class I
	Orciprenaline[115]	Class IIa
	Quinidine[8-10,15,116,117]†	Class I
Other substances	Cilostazol[118-120]	Class IIb

Recommendation: Class I: convincing evidence/opinion; Class IIa: evidence/opinion less clear; Class IIb: conflicting evidence/opinion.

*In adults an isoproterenol regimen of 0.003±0.003 μg/kg/min has been used by Ohgo et al.[15] and 0.01 to 0.02 μg/kg/min has been used by Kasanuki et al.[18]

†Aim at quinidine plasma levels of 1-3 μg/mL or 3.5-11 μmol/L.

Table 4

Diagnostic drugs in Brugada syndrome

Drug category	Drug (generic)	Use
Antiarrhythmic drugs	Ajmaline[26-29]	Maximal dose 1mg/kg
	Flecainide[30-34]*	Maximal dose 2mg/kg
	Pilsicainide[35-38]	Maximal dose 1mg/kg
	Procainamide[17,26,39,40]†	Maximal dose 10mg/kg

*It has been reported by Wolpert et al.[28] that flecainide has a 32% lower sensitivity to uncover a type-1 Brugada ECG than ajmaline

†In the first consensus report (Wilde et al.2), the sensitivity of procainamide was considered relatively low.