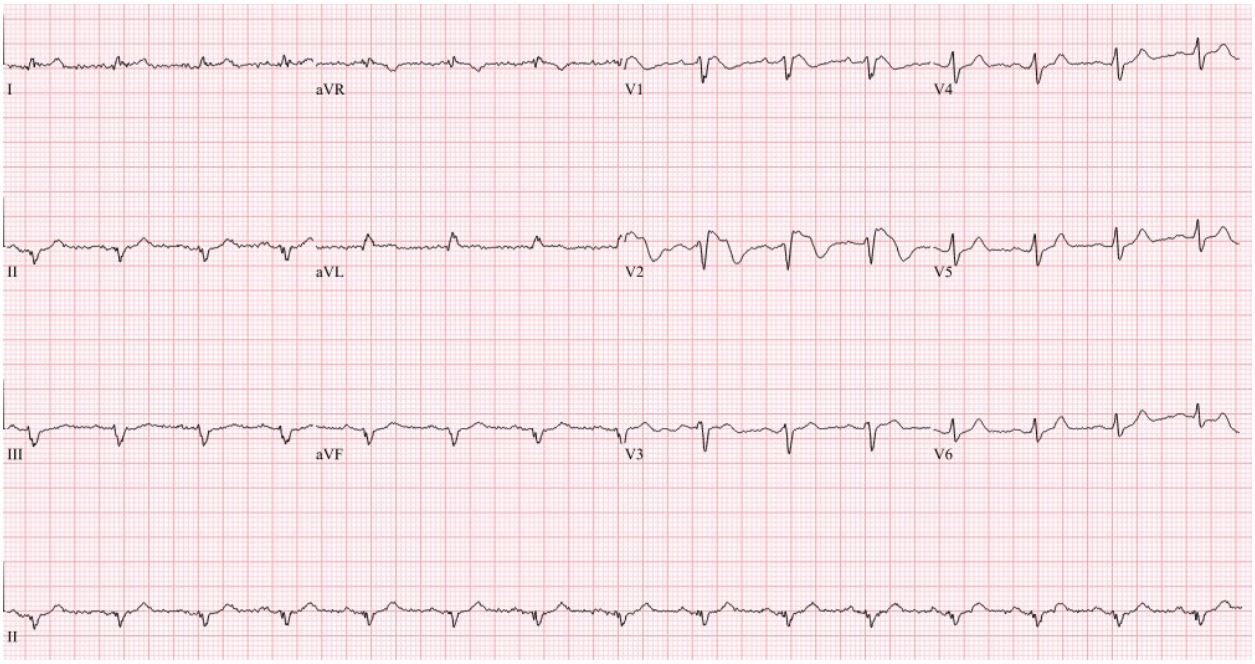
Clinical Pharmacology & Toxicology Pearl of the Week

~ Drug Induced Brugada Syndrome ~

Case:

A 71-year-old woman presented to hospital with frequent falls and altered level of consciousness after being prescribed escalating doses of carbamazepine and gabapentin over the past 4 weeks for treatment of trigeminal neuralgia. Medications also included bupropion, fluoxetine, lisdexamphetamine, conjugated estrogen, and progesterone. Carbamazepine level was 48 umol/L [normal 17-50] and the remainder of labs were non-contributory. Sedation was attributed to high doses of gabapentin. ECG revealed a new Brugada Type 1 pattern which had not been present one month earlier. Clinical Pharmacology was consulted due to suspected drug induced Brugada syndrome for medication review and deprescribing recommendations.



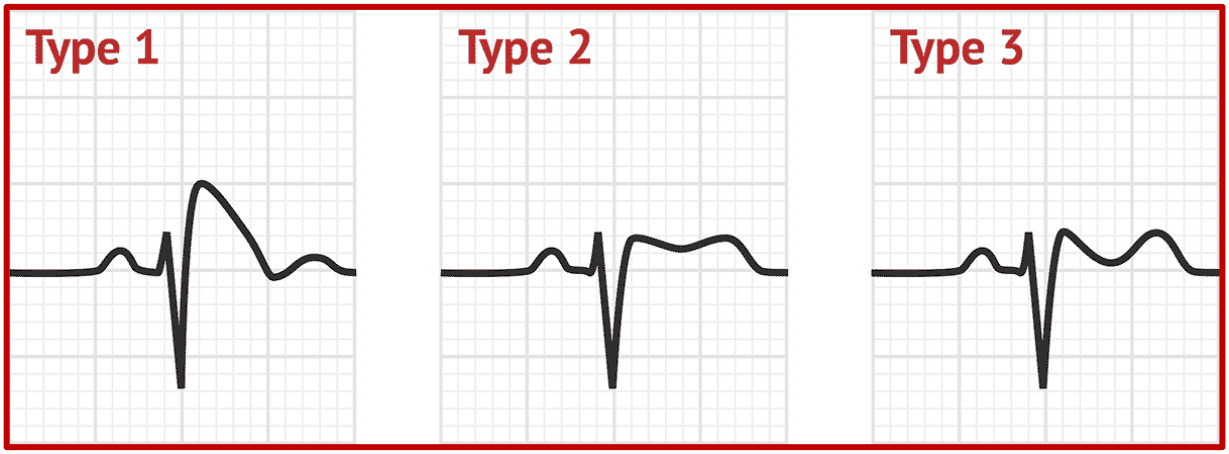
Background:

Brugada Syndrome is an inherited primary arrhythmia syndrome, predisposing patients to ventricular tachydysrhythmias and sudden cardiac death. It is 8 times more prevalent in males and is most seen in patients from Southeast Asia (Thailand, Philippines, Japan). Brugada syndrome is thought of as an autosomal dominant sodium channel disorder. However, only 30% of patients with an ECG diagnosis of Brugada Syndrome will have a confirmed SCN5A mutation decreasing sodium influx during depolarization. Other gene mutations causing decreased calcium influx or increased potassium efflux have also been identified.

Brugada Syndrome is diagnosed based on characteristic ECG patterns and responses to Class I antidysrhythmic agents. While ECG features define the condition, clinical features such as syncope history, diagnosed ventricular fibrillation and inducible dysrhythmias during EP study are more predictive of clinical outcome and mortality risk.

Diagnostic Criteria

1. A patient with ST-elevation with Type 1 (coved) morphology ≥ 2 mm in one or more right precordial leads (V_1, V_2) either spontaneously or after provocation with a Class I antiarrhythmic.
2. A patient with Type 2 (saddleback ≥ 2 mm ST elevation) or Type 3 (saddleback < 2 mm ST elevation) pattern in one or more right precordial lead (V_1, V_2) which converts to a Type I pattern after provocation with a Class I antiarrhythmic.



Drug Induced Brugada Syndrome (DIBS) is defined as the development of a Brugada pattern after exposure to an offending drug with a normal pre-treatment ECG. This is thought to be caused by modulation of cardiac conduction (generally sodium channel blockade) which exacerbates a sub-clinical genetic channelopathy.

Common Medications:

BrugadaDrugs.org is a free resource providing a comprehensive list of medications to avoid in patients with Brugada Syndrome based on evidence-based recommendations from an expert panel of cardiologists. The common feature between most of these medications is sodium channel blockade. However, some medications (e.g., bupropion, cannabis) do not have a clear mechanistic rationale.

Medications commonly encountered in Canadian practice are summarized below. “Avoid” medications are based on a documented associated between the medication and Brugada Syndrome, whereas “preferentially avoid” medications are based on a reported possible association between the medication and Brugada Syndrome. Of note, this association is with the presence of Brugada Pattern on ECG and not a patient-centered outcome such as dysrhythmia events or mortality.

Avoid		Preferentially Avoid	
Antiarrhythmics - Flecainide - Procainamide - Propafenone Analgesics - Bupivacaine - Procaine - Propofol	Psychotropics - Tricyclic Antidepressants - Oxcarbazepine - Lithium - Loxapine - Phenothiazine Antipsychotics Other - Cocaine - Ergonovine - Cannabis - Ethanol	Antiarrhythmic - Amiodarone - Propranolol - Lidocaine (systemic) - Verapamil - Vernakalant Psychotropic - Bupropion - Carbamazepine - Doxepin - Fluoxetine - Fluvoxamine Lamotrigine - Paroxetine - Phenytoin	Analgesics - Ketamine - Tramadol Other - Dimenhydrinate - Diphenhydramine - Indapamide - Metoclopramide - Edrophonium

Discussion:

Management of Drug-Induced Brugada Syndrome should involve a cardiologist with electrophysiology experience but often does not require invasive testing or interventions. The offending medication should be immediately discontinued, and daily ECGs should be followed to ensure resolution of the Brugada pattern. If the Brugada pattern is solely drug-induced, ECG should normalize with elimination of the medication (i.e., 4 to 5 half-lives). A comprehensive review of patient medications should be performed to assess for and discontinue other medications contraindicated in Brugada syndrome.

Further management of Drug-Induced Brugada Syndrome is controversial and should be guided by Electrophysiology. Risk of sudden cardiac death in Drug-Induced Brugada Syndrome is reported to be 0.08%/year, which is significantly lower than spontaneous Brugada Syndrome. However, a recent study of 32 patients with DIBS found that 34% of patients demonstrated episodic spontaneous Type I pattern on 24-hour ambulatory ECG monitoring. Rates of cardiac events were associated with the total time of Type I pattern seen on ECG in the 24-hour monitoring period. Therefore, ambulatory ECG monitoring for latent spontaneous Brugada Syndrome could be considered in these patients. However, advanced treatments for Brugada Syndrome such as ICD, RVOT ablation and quinidine are generally not indicated if the Brugada pattern resolves with medication withdrawal and patient is low risk.

Prescribing in a patient with Brugada Syndrome can be challenging due to the long list of preferentially avoided medications. Guidelines recommend avoidance of all medications on both the “avoid” and “preferentially avoid” list. Even if a patient has previously tolerated exposure to a “preferentially avoid” medication without developing ECG changes, there is not enough data to support safety. Transitioning patients to an alternative medication is preferred. However, situations may arise in which avoidance of a medication is not possible and care should be guided by a patient-centered discussion of risks and benefits. If no alternative is available and the decision was made to use a “preferentially avoid” medication, it is important to note that ECG changes are rarely seen within the first 72 hours, so ECG monitoring should be repeated at 1-2 weeks and the medication should be discontinued if a Brugada

pattern were to develop. It is important to recognize that a normal ECG does not eliminate risk as the Brugada pattern can become more apparent with fever or physiologic stress but can be used to inform the risk-benefit conversation with the patient. There is no evidence to guide the need for further ECG monitoring beyond the initial medication initiation or dose increase.

Case Resolution:

The patient was admitted to hospital and carbamazepine was stopped. ECG returned to normal by post-admission day #2. Electrophysiology was consulted and outpatient follow up was arranged to reassess the patient's ECG and discuss referral for genetic testing. On medication review, it was identified that the patient's fluoxetine and bupropion should also be discontinued, and a gradual taper plan was established for the patient to follow with their family physician. The patient was provided with a comprehensive list of medications to avoid for her records, and she was discharged from hospital on day #2 after an uncomplicated admission.

References:

1. Gray B, Kirby A, Kabunga P, Freedman SB, Yeates L, Kanthan A, Medi C, Keech A, Semsarian C, Sy RW. Twelve-lead ambulatory electrocardiographic monitoring in Brugada syndrome: potential diagnostic and prognostic implications. Heart Rhythm. 2017 Jun;14(6):866-74.
2. Priori SG, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patient with inherited primary arrhythmia syndromes. Heart Rhythm. 2013 Dec;20(12):1932-63.
3. Tisdale JE, Chung MK, Campbell KB, Hammadah M, Joglar JA, Leclerc J, Rajagopalan B. Drug-induced arrhythmias: a scientific statement from the American Heart Association. Circulation. 2020 Oct;142(15):e214-33.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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