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Ajmaline use for the Diagnosis of Brugada Syndrome

Introduction

Brugada Syndrome is an inherited cardiac disease characterised by malignant arrhythmias and sudden cardiac death. It is defined by the presence of an atypical right bundle branch block pattern with a characteristic cove-shaped ST elevation in leads V1 to V3, in the absence of obvious structural heart disease, electrolyte disturbances or ischaemia. [(1)]

The diagnostic ECG pattern in Brugada syndrome can be provoked by sodium channel blocking agents such as the Class 1 antiarrhythmics flecainide and Ajmaline.

Ajmaline is class 1a anti-arrhythmic drug with potent sodium blocking effects. It is the agent of choice for provocation tests due to its short half-life (distribution half-life 6 minutes and elimination half-life 95 minutes), established safety profile in adults and higher diagnostic yield compared with flecainide[(2-4)] Ajmaline is not licensed in Ireland.

Indication

Ajmaline is used provoke the diagnostic ECG pattern of Brugada syndrome in patients with a normal or equivocal ECG.

Target patient population

- First degree relatives of a patient with a clinical diagnosis of Brugada syndrome
- Family members of SADS victim in whom baseline ECG is suggestive (eg incomplete RBBB +/- saddle shaped ST segment elevation)
- Patients who have experienced syncopal episodes in whom ECG is suggestive (as above)
- Patients where there is a 12 lead ECG suspicious but not diagnostic of Brugada syndrome.

Contraindications and precautions for Ajmaline challenge

- Contraindicated if diagnostic criteria of Brugada Syndrome present on resting 12 Lead ECG.
- Caution in children with conduction abnormalities, since it can lead to higher degree block (sinus node disease, Mobitz Type II, Complete Heart Block, Bifascicular Block)
- Ajmaline metabolism may be impaired in liver impairment.

Target users and clinical setting

- The procedure may only be carried out in the cardiac catheterisation laboratory, or cardiac day ward with a consultant cardiologist and at least one nurse and a cardiac technician present.
- Ajmaline may only be prescribed and administered by a consultant cardiologist. Cardiopulmonary resuscitation equipment including an external defibrillator must be available.
- Resuscitation drugs must be readily available including Isoprenaline and Magnesium sulphate injection.[(6)]
- Doses of resuscitation drugs using the Drug Calculator (see below) should be calculated for each patient prior to commencement of the procedure.

Procedure for administration of Ajmaline challenge

Patient preparation

- Informed written consent, specifically mentioning the risk of arrhythmias must be taken for the Ajmaline challenge using a standard hospital consent form.
- The patient should be rested and fasting prior to the procedure. Fasting is required in case of need for resuscitation. Fasting is as per General Anaesthetic guidelines. i.e. food / milk to be stopped 6 hours prior to challenge, breastmilk 4 hours prior to challenge and clear fluids 2 hours prior to challenge.
- Any antiarrhythmic medication should be stopped prior to admission
- Electrolyte abnormalities, if suspected, should be corrected prior to the Ajmaline challenge (not necessary to check U&E prior to administration of Ajmaline if no clinical concern).
- Use a large peripheral vein as Ajmaline may be irritant. If intravenous access has been challenging (young child) and one secure IV line is obtained, it is reasonable to forego a second IV line placement (considered for resuscitation).

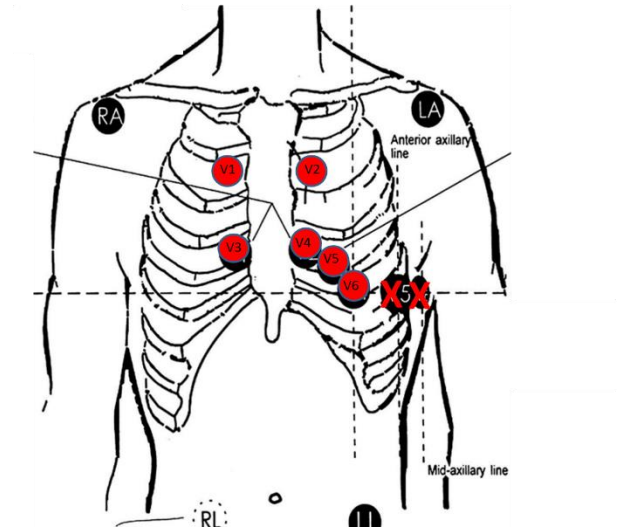
Nursing considerations

- It will be the responsibility of the nursing and medical staff (consultant) to assign roles for resuscitation prior to Ajmaline administration.
- Play therapists may provide a very useful role in distracting the child during Ajmaline administration, especially in the younger patient.
- Ensure either a Healthcare Assistant or Nurse is assigned to care for parents in the event of any emergency situation
- The Ajmaline Challenge Drug Calculator will be completed as per the patient's weight and be printed prior to Ajmaline administration.
- The Ajmaline Challenge Drug Calculator can be found on PC desktops in the individual clinical areas.
- To enable prompt treatment of ventricular arrhythmias should they arise, two bolus doses of isoprenaline and a bolus dose of magnesium sulphate will be drawn up prior to Ajmaline administration.
- The medication required for an Ajmaline challenge (Ajmaline as well as resuscitation medicines Isoprenaline and Magnesium sulphate) will be prescribed prior to administration. The Ajmaline Challenge Drug Calculator is not a prescription, all doses must be prescribed on the patient's drug kardex.
- Should an infusion of isoprenaline be required, an IV fluid chart must be ready to hand in order to accurately document the dose and volume administered.

ECG Monitoring[10]

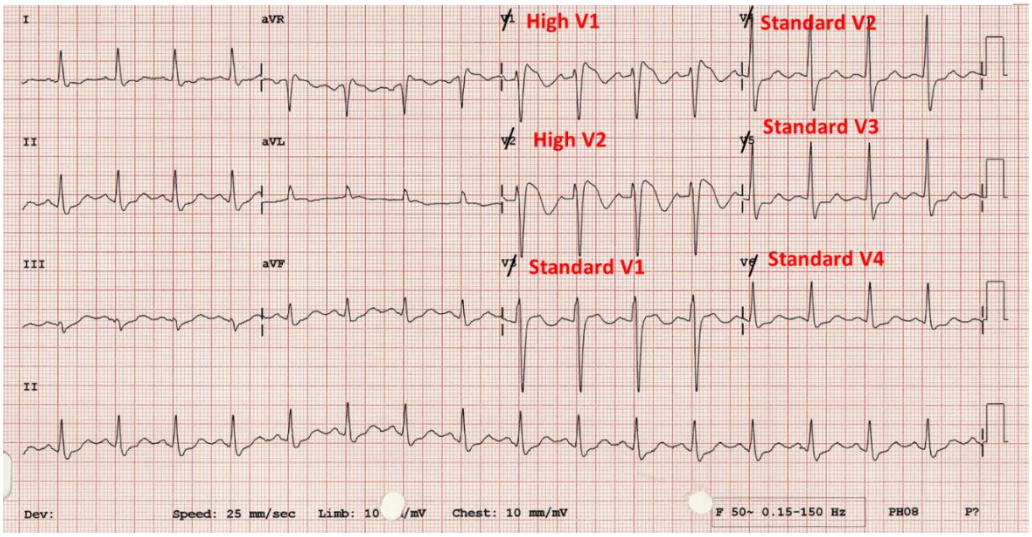
- Perform a 12- or 15- lead ECG at baseline with leads V1 and V2 in the conventional 4th intercostal space
- Change V1 to V6 two intercostal space higher – mark on the ECG V1 – high V1; V2-high V2; V3 – standard V1; V4 – standard V2; V5-standard V3; V6- standard V4; (no standard V5 or V6 unless 15-lead ECG monitor available) (Figure 1) – print a baseline ECG before Ajmaline infusion

Figure 1:



- Record ECGs every minute with high lead positions for 10 minutes total (total dose of Ajmaline infusion given in 5 minutes and continue ECG monitoring for 5 minutes post-infusion)
- Mark the high ECG lead positions on the ECG (Figure 2)

Figure 2: Ajmaline test with high ECG lead positions



Instructions for dosing, preparation and administration of Ajmaline

Ajmaline will be administered as at least five separate bolus doses (more in children weighing > 50kg). These must be given via the drug library of a designated Ajmaline Challenge B.Braun Perfusor Space pump via a three-way tap.

Prior to commencement of Ajmaline challenge

1) The Ajmaline challenge drug calculator (located on the PC desktop) must be used as an aid to confirm calculations and dilutions.
    i) Enter patient weight on the drug calculator and print calculation sheet.
    ii) Two people (one of whom must be consultant cardiologist) check and sign on the drug calculation sheet to confirm 1) entered weight and 2) ALL calculated doses are correct and in line with prescribed doses on Kardex
    iii) Should there be any discrepancies between the doses as calculated by the Ajmaline Calculator and those prescribed on the Kardex, it is the responsibility of the consultant to clarify the doses to be administered, ensuring they are in line with the recommended doses as per protocol.
    iv) Should it transpire that the issue lies with the Ajmaline Calculator, this must be immediately reported to the pharmacy department and a Medication Incident report should be submitted.

2) Ajmaline should be prescribed on the 'when required' section of the Medication Kardex. The Drug Calculation sheet is **not** a prescription.

3) Prime and pre-program pump as per Appendix 1
    a) Two people must check and sign on the drug calculation sheet for both Ajmaline that 1) **syringe preparation** and 2) **pump programming** have been carried out correctly.

4) After administration of <u>each bolus dose</u> of Ajmaline, a 5ml manual flush of Sodium Chloride 0.9%w/v will immediately follow to push the delivery of the Ajmaline to the heart. The flush will be administered via the three-way tap.

5) Documentation of administration of each dose of Ajmaline will be signed on the Medication Kardex.

Termination criteria apply (see below)

Drug	**Patient Weight**	**Dose**	**Final Concentration**	**Rate of administration**
Ajmaline 50mg/10ml ampoules **N.B.** *SEE AJMALINE CHALLENGE DRUG CALCULATOR FOR DOSES / VOLUMES TO BE ADMINISTERED*	**≤40kg**	Max cumulative dose 1mg/kg (*0.2mg/kg for five doses*)	Draw up 10ml (1 x 50mg ampoule) Ajmaline *using a filter needle.* Dilute with 10ml Glucose 5%w/v to give a final solution of **50mg/20ml (2.5mg/ml)**	Give over a minimum of five minutes via pump
	> 40kg AND <50kg ONLY	Max cumulative dose 1mg/kg (*0.2mg/kg for five doses*)	Draw up 20ml (2 x 50mg ampoules) Ajmaline *using a filter needle.* Dilute with 30ml Glucose 5%w/v to give a final concentration of **100mg/50ml (2mg/ml)**	Give over a minimum of five minutes via pump
	≥50kg ONLY Patient's weight is rounded to the nearest 10kg. *The Ajmaline Challenge Drug Calculator does this automatically (See Pump weight)*	Max cumulative dose 1mg/kg rounded to the nearest 10mg (max 100mg) *(10mg/dose, up to the total cumulative dose)*	Draw up 20ml (2 x 50mg ampoules) Ajmaline *using a filter needle*. Dilute with 30ml Glucose 5%w/v to give a final concentration of **100mg/50ml (2mg/ml)**	Give at a maximum rate of 10mg/min via pump

Sample Calculation for Ajmaline:

Patient weight: 20kg

Dose: 0.2mg/kg for five doses to a cumulative dose of 1mg/kg
= 4mg per dose for five doses, to a cumulative dose of 20mg

Draw up 10ml neat solution (1x50mg/10ml ampoule) with a filter needle and dilute with Glucose 5%w/v to give a final solution of 50mg/20ml
This gives a concentration of 2.5mg/ml
Each 4mg dose = 1.6ml (Dose in mls = $\frac{4mg \times 1)}{2.5mg}$
Total Cumulative 20mg dose = 8ml

These calculations should be checked against the Medication Kardex, and the Ajmaline Drug calculator and B.Braun pump

Side effects of Ajmaline

- Similar to all class I antiarrhythmics. Include AV block and widening of the QRS complex.
- Ventricular arrhythmias (<0.5%)[10]. Sustained ventricular arrhythmia may occur in 1.8% of adult patients with Brugada syndrome [8]. The incidence appears to be less in children[5]
- Potential risk of ventricular arrhythmia in patients that do not have Brugada syndrome particularly if Ajmaline is injected too rapidly.

Patients should be made aware of some feelings that may be experienced during the Ajmaline infusion: flushing, metallic taste in mouth, desire to pass urine[10], tingling sensation, nausea. Rarely hypotension, urticarial

Monitoring

- Continuous ECG monitoring, showing high right precordial leads (V1 – V3 in 2nd or 3rd intercostal space) is required throughout the challenge. See above.
- A baseline 12 Lead ECG (25 mm/sec) must be performed and blood pressure measurement taken and recorded.
- The challenge may be discontinued sooner if certain termination criteria are reached (see below termination criteria)
- Record 12 lead ECG every minute during Ajmaline administration and for 5 minutes afterwards, and then record every 2 minutes for 10 minutes or until return to baseline.
- Mark timing and V1/V2 positions on ECG.
- Record blood pressure at 30 minutes and 1 hour after last dose.
- Record ECG one hour after last dose.

Termination criteria

- Target dose of Ajmaline 1mg/kg or maximum dose (100mg) is reached.
- Consider termination of test if QRS prolongation of > 30% compared to baseline (occurs in up to 50% of all tested subjects)[13]
- Occurrence of frequent premature ventricular ectopics, ventricular tachycardia, sinus arrest or 2nd/ 3rd degree AV block
- Diagnostic ECG pattern of Brugada Syndrome in at least one right precordial lead.
- Occurrence of J-point elevation or ST segment elevation > 2mm.[14]

Criteria for positive test[14]

Brugada Syndrome is diagnosed if characteristic ECG changes are present. These include;

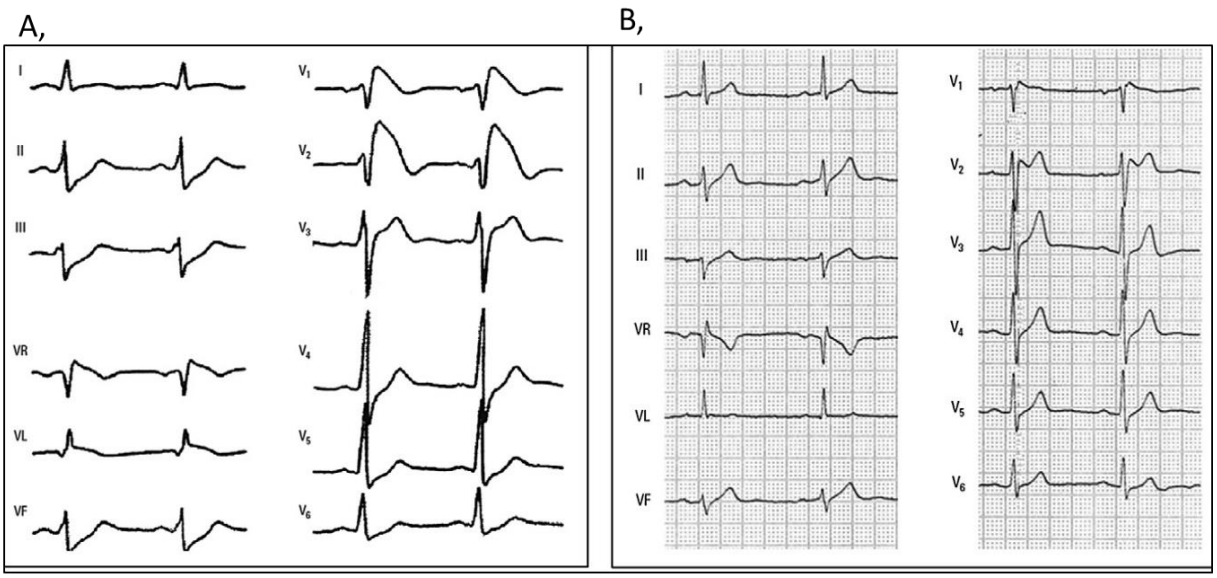
- RBBB pattern with coved-type ST elevation in two leads of V1-V3.
- R wave / J point elevation ≥ 2mm.
- Ventricular tachycardia.

ECG diagnostic criteria of Brugada syndrome[10]

- ST segment elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.
- Patients with type 2 or type 3 ST segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type 1 ECG morphology.

In the **new ECG criteria**, there are **only 2 types** of ECG patterns considered, type 1 is identical to classic type 1 and type 2 joins together the pattern 2 and 3 (Figure 3).

Figure 3: A - Typical type 1 Brugada pattern B - Typical type 2 Brugada pattern:



Post test

- Patients who have a positive test or who experience arrhythmias during the test will be admitted to the hospital.
- If the test is negative patient returns to Medical Day Ward for monitoring (or remains on the day ward if this is where the test occurred).
- All patients require an ECG one hour after completion of Ajmaline challenge.
- Monitor heart rate, BP every 30 minutes for 2 hours.

Discharge criteria

- Patient may be discharged following repeat 12 lead ECG and review by Cardiology.

Dosing and administration of resuscitation drugs

If ventricular arrhythmias are observed, treatment is with

1) Two bolus doses of Isoprenaline
2) One bolus dose of Magnesium Sulphate.
3) Isoprenaline infusion will then be commenced if required

Prior to the commencement of the challenge:

- Two bolus doses of Isoprenaline and one bolus dose of Magnesium Sulphate will be drawn up and ready for administration (see instructions in tables below)
- All prescriptions will be charted on the medication kardex:
    - When required section:
        - Isoprenaline bolus dose x 2
        - Magnesium Sulphate bolus dose x 1
    - Intravenous infusions section:
        - Isoprenaline infusion
- The Ajmaline Challenge drug calculator will be used as a tool to aid calculations and dilution.

Instructions for Dosing, Preparation and Administration of Isoprenaline

Prior to commencement of Ajmaline challenge

1) Ensure Ajmaline Challenge drug calculation sheet is printed and top section signed (one of signatures must be a consultant cardiologist) to confirm 1) entered weight and 2) ALL calculated doses are correct and in line with prescribed doses on Kardex
2) Should there be any discrepancies between the doses as calculated by the Ajmaline Calculator and those prescribed on the Kardex, it is the responsibility of the consultant to clarify the doses to be administered, ensuring they are in line with the recommended doses as per protocol.
3) Should it transpire that the issue lies with the Ajmaline Calculator, this must be immediately reported to the pharmacy department. A Medication Incident report should also be submitted.
4) For all patients an initial 1mg/50ml isoprenaline solution is made up (See table below for instructions).
5) From the 1mg/50ml solution, withdraw two bolus doses (1 microgram/kg (Max 20 micrograms)) of Isoprenaline and leave ready for use in a blue tray. (Refer to drug calculator for correct volumes)
6) Load the remaining solution into a second B.Braun Perfusor Infusion pump.
7) Prime and pre-program pump as per Appendix 1
    a) Two people must check and sign on the drug calculation sheet that 1) **syringe preparation** and 2) **pump programming** have been carried out correctly.
    b) The prep / pump check is also signed on the intravenous infusion section of the patient's Medication Kardex.
8) Prepare and label two sodium chloride 0.9% w/v flushes and leave ready for use in blue tray.
9) It is important that an IV fluid Chart is ready to hand should an infusion of isoprenaline be required, in order to accurately document the dose and volume administered.

Drug	Dose	Final Concentration	Compatible with	Rate of administration
Isoprenaline 1mg/5ml ampoules **N.B. SEE AJMALINE CHALLENGE DRUG CALCULATOR FOR DOSES / VOLUMES TO BE ADMINISTERED**	**Bolus dose (off-label use):** 1 microgram/kg (Max 20 microgram) **Continuous infusion:** *Note: An infusion will only be needed where 2xbolus doses have not been successful in resuming normal sinus rhythm* Default Start dose is 1microgram/kg/min (maximum 20 micrograms/minute) This is the upper normal dosing range and should be reduced once normal sinus rhythm is restored.	**Bolus dose:** • Draw up 5ml (1mg). • Dilute to a final volume of 50ml in a syringe. • This gives a concentration of 1mg/50ml (20 microgram/ml) • The bolus doses are drawn from this syringe. **Continuous infusion:** • Commence infusion using the remainder of the 1mg/50ml solution. • Should a further ongoing continuous infusion be required refer to Ajmaline Challenge drug calculator. • The volumes displayed should be used to aid selection of the most appropriate concentration. (1mg/50ml, 3mg/50ml or 6mg/50ml) - this should usually be based on an infusion duration of two hours • All doses will be capped at 20 micrograms/ minute • N.B: The most dilute concentration should be used Only select the more concentrated solutions for heavier patients on higher doses	Sodium Chloride 0.9%w/v or Glucose 5% w/v. **Note**: Glucose is the preferred diluent due to the acidic nature of isporenaline. Monitor for potential venous irritation	**Bolus dose:** Administered as a bolus over at least one minute. A further bolus may be administered after one minute and a continuous infusion may then be commenced if needed **Continuous infusion:** Administered at a rate of 0.1 – 1 microgram/kg/min. **Maximum rate 20 micrograms/minute** Adjusted according to patient's response (target being 20% increase in heart rate)

Instructions for Dosing, Preparation and Administration of Magnesium Sulphate 50%w/v

- Ensure Ajmaline Challenge drug calculation sheet is printed and top section signed (one of signatures must be a consultant cardiologist) to confirm 1) entered weight and 2) ALL calculated doses are correct and in line with prescribed doses on Kardex
- Should there be any discrepancies between the doses as calculated by the Ajmaline Calculator and those prescribed on the Kardex, it is the responsibility of the consultant to clarify the doses to be administered, ensuring they are in line with the recommended doses as per protocol.
- Should it transpire that the issue lies with the Ajmaline Calculator, this must be immediately reported to the pharmacy department and a Medication Incident report should be submitted.
- A bolus dose should be prepared and labelled for all patients prior to commencement of Ajmaline Challenge. See table below for dosing instructions. Refer to Ajmaline Challenge Drug Calculator for volumes to be administered.

- Leave ready for use in a blue tray separate from the Isoprenaline bolus doses.
- A sodium chloride 0.9% w/v flush should also be prepared and labelled.

Drug	Dose	Final Concentration	Compatible with	Rate of administration
Magnesium Sulphate 50% w/v (2mmol/ml or 500mg/ml) **N.B. SEE AJMALINE CHALLENGE DRUG CALCULATOR FOR DOSES / VOLUMES TO BE ADMINISTERED**	0.2mmol/kg (50mg/kg). Max 8mmol (2g)	• **Must be diluted prior to use** • Maximum concentration 0.4mmol/ml. • Calculate the required volume of Magnesium Sulphate and dilute to **at least** five times this volume i.e. Every 1mL (2mmol) of magnesium sulphate 50%w/v injection should be diluted to at least 5mL with infusion fluid to give a final concentration of 0.4mmol/ml (100mg/ml) magnesium sulphate **NOTE**: More dilute solutions should be used where appropriate. Magnesium has a high osmolarity and may cause tissue damage if it extravasates into the surrounding tissue. If given peripherally, monitor for signs of phlebitis.	Sodium Chloride 0.9%w/v or Glucose 5% w/v	Give as a slow IV push over 5 minutes **Maximum rate of administration is 0.04mmol/kg/min (10mg/kg/min)**

Quinidine sulphate

Quinidine sulphate has been used in adults (200mg po every 2 hours up to a max of 1.2g/day) if isoprenaline has been ineffective in controlling ventricular arrhythmias.

Paediatric dosing for arrhythmias (*reference Lexicomp*)

***Arrhythmias: Children and Adolescents: Limited data available*:**

- Oral: Quinidine sulphate immediate release: Usual: 30 mg/kg/day or 900 mg/m2/day in 5 daily doses or 6 mg/kg every 4-6 hours;
- Range: 15-60 mg/kg/day in 4-5 divided doses; usual maximum dose: 600 mg; maximum daily dose: 3000-4000 mg/day

Link to References

Link to Ajmaline Challenge Programming Algorithms