

## **Drug-induced Arrhythmia Risk Evaluation: The DARE Study Hospital Doctor Information Sheet**

**Background:** As you know, Torsade de Pointes, ventricular fibrillation and occasionally monomorphic ventricular tachycardia are well-recognised complications of cardiac and non-cardiac drug treatment. Recently both Triludan (terfenadine) and Prepulsid (cisapride) have been withdrawn from the market due to reports of proarrhythmia and related deaths. The phenomenon is rare but the understanding of its epidemiological and clinical importance in the UK and worldwide is limited by the nature of the reporting of these incidents. There is a reliance on spontaneous and anecdotal accounts without systematic analysis. Misreporting and underreporting of cases is also problematic. There is difficulty in attributing events such as presyncope, syncope and sudden death, to drug therapy, due to the clinical complexity of retrospective diagnosis. In addition these events are not easily predictable and can appear highly idiosyncratic. Proarrhythmia is therefore an issue of great concern.

Various clinical factors appear to predispose individuals to developing the condition i.e. female sex, structural cardiac disease, metabolic abnormalities and systemic and cerebrovascular disease. In addition myocardial sodium and potassium ion channel mutations have been described in the inherited conditions associated with these arrhythmias: the long QT and Brugada syndromes.

**Aims:** The study divides into epidemiological and genetic components:

- The epidemiological study aims:
  1. To assess the importance of this condition throughout England.
  2. To provide data on those drugs contributing most significantly to the public health issue.
  3. To determine the outcome of patients in terms of cardiac events and mortality compared to a control group.
  4. To determine the relative risk of acknowledged predisposing factors.
- The genetic study aims:
  1. To demonstrate that the above-mentioned mutations are commoner in a population suffering proarrhythmia compared to a control group.
  2. To determine the relative risk of genotype.

If the study proves the association of proarrhythmia with carrier status, a separate future project will be pursued to assess penetrance i.e. the relationship between phenotype and mutation carriage in a pedigree. Families of probands in whom a disease causing mutation has been identified will therefore be offered screening and counselling, provided the proband has agreed to their involvement.

We thus expect to further our understanding of this rare but important serious adverse drug reaction. This will contribute to the safer development and prescription of drugs and improve the prediction of future proarrhythmic risk for other patients and their families.

## **Drug-induced Arrhythmia Risk Evaluation: The DARE Study Hospital Doctor Protocol Sheet**

**Case Recruitment:** Patients who have suffered a proarrhythmic event will be recruited over a 5 year period via referrals from cardiologists and electrophysiologists, such as yourself, based in England. The inclusion criteria require **at least one** of the following diagnosed as secondary to therapeutic drug administration or overdose:

- Documented TdP, VF, polymorphic VT or non-polymorphic VT (see VT criteria)
- Exacerbation of an already existent ventricular arrhythmia
- Severe QT prolongation (corrected QT interval  $\geq 500$ ms)
- QT interval prolongation (corrected QT interval  $\geq 450$ ms [male patient] or  $\geq 470$ ms [female patient] **and** a clinical history of presyncope or syncope)

(Notes on case exclusion criteria and criteria for VT are appended to this document)

We request that you ask appropriate patients who are agreeable to participating to return a card (supplied by us) to the Drug Safety Research Unit (DSRU) to demonstrate consent to be contacted and to facilitate an interview at the patient's home. We will also supply information sheets for you to pass on to the patient to read in the meantime.

**Case Assessment:** Each individual will be assessed locally by a research nurse to discuss consent and then provide historical detail and an ECG. Provided the patient is 16 years old or more, a blood sample for DNA analysis will be consented for specifically to allow discussion of the ethical issues. If the individual refuses to give blood they will still be included in the study. We also consent for permission to examine their GP medical records and for copies of relevant medical notes from their hospital admission (provided you are agreeable). If your patient enrolls you will be informed of his/her results if they agree. Otherwise strictest confidentiality will be maintained.

**Control Recruitment and Assessment:** We will approach GPs of patients for their co-operation to recruit controls from their patient lists in order to have as relevant a comparison for each case. The individuals should be sex and age matched and we suggest that the closest 12 individuals be approached for their consent to be seen. This would be indicated by returning a 'consent to contact' card. They will also receive an information sheet. The four best age-matched individuals who respond within 4 weeks by returning a card to the DSRU will be contacted. A short interview will be arranged involving discussion of consent, an ECG if feasible and permission to examine GP records. Again there will be specific consent for a blood sample. In order to eliminate the possibility of harming the controls by performing gene testing in otherwise asymptomatic and unaffected individuals, results will not be relayed to them under any circumstances. If the ECG demonstrates incidentally a significant medical condition, we will, with the patient's permission, relay a copy and report of the ECG to the GP.

**Clinical Analysis and Follow-up:** Data from both groups will be recorded and stored at St. George's and the Drug Safety Research Unit (DSRU) under anonymous codes. The only data linking code to name will be stored separately at the DSRU.

This will allow annual follow-up of these individuals over the 5-year period without linking DNA results to names. We will first ensure that the individuals are alive via The General Register Office and by contacting GPs' surgeries. If they have died we will ask their GP for permission to release their records for our review. Otherwise we will contact the patient directly. If any morbidity has occurred we will approach the GP for data and if necessary the relevant hospital for further information.

**DNA Analysis:** Blood samples will be stored under anonymous codes at St. George's Hospital. Each blood sample will be analysed for abnormalities in the cardiac sodium and potassium ion channel genes implicated in Long QT and Brugada Syndromes. No other genes will be examined for unless a new gene is discovered in the future that appears to be potentially causative in proarrhythmia and the Long QT and Brugada syndromes e.g. cardiac calcium channel mutations. The DNA controls will be derived from the epidemiological controls and departmental DNA libraries.

**Patient's DNA Results – Case Patients:** If patients do not wish to be told any DNA results this will be respected. Patients with identified mutations, who wish to be informed of their results, will be asked if they would like to attend St George's Hospital for genetic counselling and advice. If this is not possible it can be arranged nearer to their home. The results will only be relayed to you and their GP if they have consented, and we may suggest additional treatment.

**Statistical Analysis:** Mortality and cardiovascular morbidity data of the proarrhythmia and control groups will be compared for a statistically significant difference using conditional logistic regression. A similar analysis will also examine the acknowledged predisposing clinical risk factors and group frequencies of the relevant mutations. This will generate results in the form of relative risks. The genetic study will look for a significant difference in carrier status between the two groups and the associated relative risk.

**Family DNA Studies:** Any patients with definite disease causing mutations, who have asked to be informed of their results, will have been asked if their families may be contacted for a potential future study examining the relationship between genetic and clinical status. This is dependent on the study establishing an association between genotype and proarrhythmia. Consent, however, can be withdrawn at any time and relatives will have to give their own separate agreement.

**Clinical Implications:** Enrolled patients with confirmed proarrhythmia will receive drug avoidance advice e.g. torsadogenic agents. Some cases may demonstrate a previously undiagnosed phenotype (e.g. overt long QT or Brugada syndromes) or a mutation may be identified that carries high future risk. Provided the individual consents we will instigate appropriate management locally under your supervision. This could involve medication and/or an ICD or permanent pacemaker.

# NOTES ON CASE EXCLUSION CRITERIA

Particular attention will be paid to adequate exclusion of other aetiologies for arrhythmias (not drug-induced):

Not diagnosed as secondary to therapeutic drug administration or O/D\*

**or**

No documented TdP, VF, polymorphic VT or non-polymorphic VT\*\*

**and/or**

No exacerbation of pre-existing ventricular arrhythmia

**and/or**

QTc interval < 500ms - Except if <450ms [male] or 470ms [female] with a clinical history of presyncope or syncope

**NB** Children < 16 years old will be excluded from the genetics project

## \*Ventricular arrhythmia as a result of chronic structural heart disease or acute ischaemia but not drug related

An SGHMS Review Panel will consider the following factors before including a case:

- previous history
- investigation results (e.g. cardiac enzymes, ECG, echocardiography, cardiac catheterisation)
- timing of drug administration
- timing of ischaemic event (> 48 hours)

If the diagnosis of drug-induced arrhythmia is possible but unclear then the study team would still wish to recruit and assess the patient directly.

## \*\*VT – how many beats are required for study inclusion?

- polymorphic VT of  $\geq 5$  beats

**and/or**

- sustained monomorphic VT (at least 30 sec or requiring emergency intervention)