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Short QT syndrome in infancy. Therapeutic drug monitoring of hydroquinidine in a newborn infant.

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Here we describe our five years experience on use of oral hydroquinidine (HQ) in a newborn with familiar Short QT Syndrome (SQTS).

In July 2005 a female child with history of SQTS in her family was born in Turin, Italy. She was the first-born daughter of a patient with SQTS and history of syncope during exertion and paroxysmal atrial fibrillation since 20 years of age, belonging to a family with many cases of sudden death in four generations and also in the newborn [1]. The family was genotyped and a mis-sense mutation causing the substitution of asparagine for a positively charged lysine at codon 588 (N588K) in the S5-loop region of the cardiac $K_V11.1^*$ channel KCNH2 (HERG) was found [2]. The effect of the mutation is to increase the repolarizing currents active during the early phase of the action potential, leading to abbreviation of the action potential and thus to abbreviation of the QT interval. Moreover it reduces the affinity of the channel for drugs with K_{IR} blocking action, such as sotalol, but to a lesser degree for hydroquinidine [3,4].

Twelve-lead standard electrocardiogram (ECG) recordings was obtained at birth and was consistent with the diagnosis (QTc 310 msec). During the first two weeks of life ECG recordings was repeated every two days. After discharge from hospital, ECG was repeated at each ambulatory follow up (Figure 1). Periodically ambulatory ECG monitoring (24 hours Holter) was also performed.

She was recognized as being affected by the N588K mutation in KCNH2 (HERG), already identified in the father and in other family members.

Antiarrhythmic prophylaxis with oral HQ was started at nine days of age. Drug dosage was increased every week, monitoring ECG and plasma level of basal HQ (quantified by HPLC-UV). The target was a QTc interval at ECG ≥ 360 msec and HQ basal plasma level between 0.6 and 2.0 μg/ml (therapeutic range referred from literature). Initial oral drug dosage was 4 mg/kg three times daily, while maximum dosage administered to maintain HQ in therapeutic range was 10.9 mg/kg three times daily. The mean HQ plasma level achieved was 0.66 μg/ml ± 0.23 (range 0.27-1.14). HQ dosage pro kg, QTc and HQ plasma levels are summarized in Table 1. A significant correlation

between HQ plasma levels and prolongation of QT interval was observed. No correlation was found between HQ plasma levels and drug dosage.

No cardiac symptoms or major side effect were observed during a follow up of five years. Only transient abdominal pain was observed for a few days after every increase of drug dosage. During periodical Holter monitoring no arrhythmic events were recorded.

SQTS is a rare, recently recognized genetic anomaly [5], characterized by a typical electrocardiogram (ECG) pattern and the risk of major, sometimes lethal, arrhythmias. The ECG shows a short QTc interval (less than 320 msec), with lack of adaptation during increase of heart rate. Arrhythmias associated with SQTS are atrial fibrillation and ventricular tachyarrhythmias. Sudden cardiac death occurs in adult patients and also in infancy, so SQTS is a potential cause of Sudden Infant Death Syndrome.

To date less then eighty patients with SQTS are described in literature and most of them are familiar forms. In 2000 a family (a 17-year-old girl with several episodes of paroxysmal atrial fibrillation, her brother, and their mother) with QT and QTc intervals < 300 ms was described [5]. In 2003 the short QT syndrome was recognized as a new clinical entity related to familial sudden_death [1]. Cardiac arrest is the most frequent clinical presentation. SQTS was soon recognized as a genetic disorder with autosomal dominant inheritance. Gain of function mutations in three different genes (KCNH2, KCNQ1, KCNJ2) encoding potassium channels and loss of functions mutations in two genes encoding the $Ca_V1.2^*$ calcium channel (CACNA1C and CACNB2b), have been linked with SQTS [6,7].

Because of the high incidence of sudden death, the first-choice therapy in adult patients with SQTS is an implantable cardioverter-defibrillator device (ICD) [8]. In paediatric patients there are technical problems and risk of complications linked to ICD implant: in small babies ICD implant is not feasible, so pharmacological prophylaxis is the only alternative. Medical treatment proposed for SQTS is oral HQ, the only antiarrhythmic drug able to normalize the QT interval at resting heart rates [3,4,9].

HQ therapy may induce many different adverse effects both cardiac and not. Thus, monitoring of its plasma levels in treated patients may be useful to avoid toxicity. Up to now data about therapeutic HQ monitoring in patients are rarely available in literature, even less about paediatric patients.

The case of this infant well explains why therapeutic drug monitoring is considered an important tool in clinical practice in different disciplines. In newborn babies is often difficult to obtain an ECG with heart rate less than 100 beats/min and the correct QT evaluation is not always reliable. So it seems to be strategical to avoid an erroneous HQ dosage by monitoring drug plasma concentration. An increase in drug biotransformation ability reached by liver during the first months of life is probably responsible for the need of greater doses of HQ for maintaining therapeutic plasma concentrations.

*Channels nomenclature conforms to BJP's Guide: Alexander SPH, Mathie A, Peters JA (2009). Guide to Receptors and Channels (GRAC), 4th edn. *Br J Pharmacol***158** (Suppl. 1): S1–S254.

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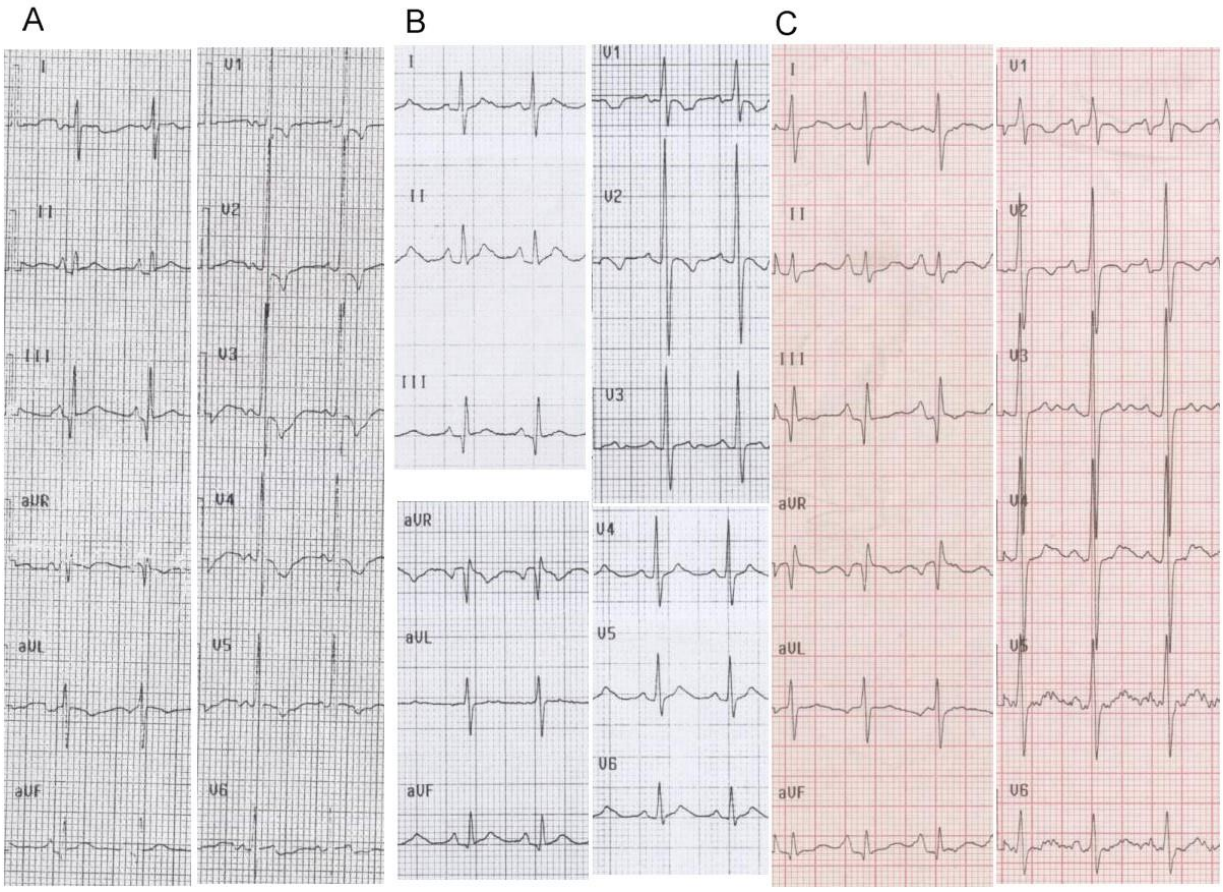

Figure 1

Representative twelve-lead ECGs at birth (A), at one year of age (B) and at five years (C). QTc at birth 310 ms (A), at one year 390 ms (B), at five years 400 ms (C), paper speed 25mm/s.

Table 1

Hydroquinidine (HQ) dosage, plasma concentrations and QTc measurements

Age (months)	HQ dosage (mg/kg)	HQ Plasma level (μg/ml)	QTc (ms)
0.5	4	-	310
1	4	0.725	430
4	5	0.267	340
4.5	5.8	0.751	370
7	8	0.335	340
7.5	8.5	0.640	360
12	8.3	0.475	390
15	9	0.480	370
17	10	0.777	400
24	10.9	0.685	380
27	9.2	1.142	420
38	10	0.708	430
51	9.5	0.761	400
60	8.5	0.861	420