Letter to the Editors

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

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Here we describe our 5 years' experience on the use of oral hydroquinidine (HQ) in a newborn with familiar short QT syndrome (SQTS).

In July 2005 a female child with a 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 were obtained at birth and were consistent with the diagnosis (QT_c 310 ms). During the first 2 weeks of life ECG recordings was repeated every 2 days. After discharge from hospital, ECG was repeated at each ambulatory follow-up (Figure 1). Periodically ambulatory ECG monitoring (24 h 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.

Anti-arrhythmic prophylaxis with oral HQ was started at 9 days of age. Drug dosage was increased every week, monitoring ECG and plasma concentration of basal HQ (quantified by HPLC-UV). The target was a QT_c interval at ECG ≥ 360 ms and HQ basal plasma concentration between 0.6 and 2.0 $\mu\text{g ml}^{-1}$ (therapeutic range referred from literature). Initial oral drug dosage was 4 mg kg^{-1} three times daily, while maximum dosage administered to maintain HQ in therapeutic range was 10.9 mg kg^{-1} three times daily. The mean HQ plasma concentration achieved was $0.66 \pm 0.23 \mu\text{g ml}^{-1}$ (range 0.27–1.14). HQ dosage kg^{-1} , QT_c and HQ plasma concentrations are summarized in Table 1. A significant correlation between HQ plasma concentrations and prolongation of QT interval was observed. No correlation was found between HQ plasma concentrations and drug dosage.

No cardiac symptoms or major side effect were observed during a follow-up of 5 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 QT_c interval (less than 320 ms), 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 than 80 patients with SQTS are described in the 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 QT_c intervals <300 ms was described [5]. In 2003 the

*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.

Figure 1

Representative twelve-lead ECGs at birth (A), at 1 year of age (B) and at 5 years (C). QT_c at birth 310 ms (A), at 1 year 390 ms (B), at 5 years 400 ms (C), paper speed 25 mm s⁻¹

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 function 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 an ICD implant: in small babies an ICD implant is not feasible, so pharmacological prophylaxis is the only alternative. Medical treatment proposed for SQTs is oral HQ, the only anti-arrhythmic 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 concentrations 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 a heart rate less than 100 beats min⁻¹ 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.

Table 1

Hydroquinidine (HQ) dosage, plasma concentrations and QT_c measurements

Age (months)	HQ dosage (mg kg ⁻¹)	HQ plasma concentration (μg ml ⁻¹)	QT _c (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

Competing Interests

There are no competing interests to declare.

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