Effect of halofantrine on QT interval in children

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In order to assess cardiac tolerance of halofantrine in children, we studied, retrospectively, 15 non complicated falciparum malaria cases treated with halofantrine, and focused on the effect on ventricular repolarisation. Our data showed that halofantrine can produce a moderate QTc prolongation without any life-threatening arrhythmia. As long as contraindications of the drug are respected, this treatment should be considered as a therapeutical option in young children presenting with non complicated falciparum malaria.

Keywords: Halofantrine, QT interval, Malaria, Children

Malaria remains one of the major causes of infectious diseases and non-endemic countries are exposed to imported malaria. In the case of acute malaria an early curative treatment is necessary. In France, five drugs are labelled for treatment of falciparum malaria in children: atovaquone-proguanil, halofantrine, mefloquine, quinine, and artemether-lumefantrine. Since 1993, halofantrine has been reported to have cardiac side-effects and to increase QT interval in several studies in adults. Few studies have established parameters of QT interval in children; when they are treated with halofantrine, increased QTc is common but serious side effects are very rare. Nevertheless, the use of halofantrine in children has dramatically decreased.

In order to assess tolerance of halofantrine in children, we studied retrospectively non-complicated falciparum malaria patients treated with halofantrine, and focused on its effect on ventricular repolarisation.

In 15 children (mean age 8 years, range 3 months to 16 years) referred for acute falciparum malaria and treated with recommended doses of halofantrine in children, i.e. 8 mg/kg every 6 hours for three doses, we performed ECGs before halofantrine treatment and within 18 hours after the course. Actually, the maximum QTc is noted between 16 and 24 hours after the first dose of halofantrine. The ECGs were acquired on a digital ECG and measured manually. We used the Bazett formula to correct QT for heart rate ($QTc = QT / (RR)^{1/2}$). All the ECGs were analysed by two different persons. When the results were

different, the mean value of the two results was chosen. The mean baseline QTc was 410 ± 24 milliseconds (range 363–432 milliseconds). The mean QTc interval after halofantrine was 441 ± 31 milliseconds (range 395–507 milliseconds). Difference of the means was statistically significant ($P=0.0047$; Mann–Whitney test). The QTc varied from -23 to $+100$ milliseconds under treatment and five children out of 15 (33%) had a QTc >440 milliseconds (Table 1). Mean and standard error of mean of QTc variation were 31.8 and 9.6 milliseconds, respectively. None of these children who were seen on day 3 and day 28 for assessment of parasitemia presented with any cardiac symptoms and all of them recovered from malaria.

Severe complications have rarely been reported in children: Nosten *et al.*¹ reports the case of a boy who lost consciousness for several minutes after receiving a high dose of halofantrine (72 mg/kg) after mefloquine administration, which may enhance the cardiotoxicity of halofantrine. Akhtar and Imran² report the death of a 2-year-old boy weighing only 8 kg, who had presented vomiting and diarrhoea for 18 days; sudden death occurred before any kalemia assessment or ECG was performed. QTc prolongation and ventricular arrhythmia reported by Lavallée *et al.*³ were not life threatening and disappeared after some days. In 2009, a review of fatal cardiotoxicity related to halofantrine, based on a worldwide safety data base, identified five deaths in children. All had previous contraindications to halofantrine.⁴

Halofantrine is only available for oral use and this drug should not be taken with food. Peak plasma concentration is achieved in 4–8 hours after an oral dose and the elimination half-life is 1–5 days for the parent drug and 3–7 days for the active metabolite

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Table 1 ECG measurements at baseline and after treatment

No.	Baseline ECG			Post-halofantrine ECG			Delta QTc (millisecond)
	QT (second)	RR (second)	QTc (millisecond)	QT (second)	RR (second)	QTc (millisecond)	
1	0.312	0.520	432	0.300	0.500	424	−8
2	0.288	0.460	424	0.360	0.680	436	+12
3	0.320	0.624	405	0.340	0.620	431	+26
4	0.248	0.460	365	0.348	0.560	465	+100
5	0.300	0.680	363	0.420	0.840	458	+95
6	0.280	0.500	395	0.320	0.608	410	+15
7	0.280	0.448	418	0.328	0.560	438	+20
8	0.300	0.500	424	0.380	0.560	507	+83
9	0.340	0.660	418	0.344	0.756	395	−23
10	0.360	0.740	418	0.380	0.680	460	+42
11	0.280	0.448	418	0.320	0.540	435	+17
12	0.300	0.552	403	0.360	0.560	481	+78
13	0.328	0.680	397	0.400	1.04	392	−5
14	0.280	0.448	418	0.328	0.568	435	+17
15	0.300	0.504	408	0.300	0.520	416	+8

Note: $QTc = QT / (RR)^{1/2}$.

QTc values >440 milliseconds are in bold.

N-desbutylhalofantrine. Halofantrine blocks HERG current (I_{kr}) that initiates repolarization and determine the QT interval in a concentration-dependent manner.⁵

Halofantrine is the only available anti-malaria drug with a paediatric formulation (syrup with a banana-vanilla aroma). In children under 6 years, tablets of other anti-malarial drugs must be crushed; taste becomes very unpleasant, which may enhance vomiting due to malaria. In agreement with the literature, our data showed that halofantrine can produce a moderate QTc prolongation. However, no life-threatening arrhythmia was observed in this cohort. Moreover, no clinical cardiac complication occurred in any of the 180 children successfully treated with halofantrine in our hospital before the present study (10% relapsed and recovered with a second cure of halofantrine).

We suggest ECG monitoring in children to detect transient ECG anomalies. Furthermore, follow-up of QTc in pediatric patients should be completed by systematic ECG between 16 and 24 hours after the first administration of halofantrine. If QTc is more than 440 milliseconds and less than 500 milliseconds, an ECG should be performed 3 days after the end of treatment. In the case of the QTc>500 milliseconds,

then further intake of halofantrine should be carefully considered.

As long as contraindications of the drug (QTc>440 milliseconds before treatment, family history of long QT syndrome or unexplained young sudden death, personal history of unexplained syncope) and rules of prescription are respected, and risk factors for QTc prolongation (electrolyte imbalance, thiamine deficiency, previous administration of mefloquine or other drugs that prolong QT interval and maybe female gender) are taken into account, this treatment should be considered as a therapeutically option in young children presenting with acute malaria.

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