Cardiology in the Young

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Amiodarone–sirolimus interaction in a neonate with tuberous sclerosis complex

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Brief Report

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Background

Tuberous sclerosis complex is a genetic condition with multiple organ manifestations, including the heart.[1] Cardiac rhabdomyomas may be detected in utero or after birth. Typically, these lesions regress spontaneously. However, they can cause life-threatening left or right outflow tract obstruction and arrhythmia, depending on size and localisation, prompting poor neonatal outcome. mTOR inhibitors, such as everolimus or sirolimus, may represent a causative treatment option in individuals with tuberous sclerosis complex. Nevertheless, these drugs are currently only approved for other tuberous sclerosis complex manifestations, for example, giant cell astrocytomas, pulmonary lymphangioleiomyomatosis, and refractory epilepsy. Amiodarone (Class III antiarrhythmic agent) represents a symptomatic treatment for control of ventricular and supraventricular arrhythmias. Concomitant administration of amiodarone and sirolimus may result in increased sirolimus levels in paediatric heart transplant patients, possibly due to inhibition of sirolimus metabolism through CYP3A4 by amiodarone.[2] There are many cases reporting off-label treatment with mTOR inhibitors for tuberous sclerosis complex-related cardiac rhabdomyomas in the literature.[3] To our knowledge, there is no report on treatment with sirolimus and amiodarone for cardiac rhabdomyomas-associated arrhythmias in tuberous sclerosis complex neonates.

Case report

A 35-year-old female gave vaginal birth to a female infant at 38 + 6 weeks gestational age after the detection of fetal arrhythmias. Birth weight was 3.25 kg (68th percentile), and Apgar scores were 8, 9, and 10 at 1, 5, and 10 min, respectively. After good adaptation initially, the infant presented with distress and supraventricular tachycardia (260 bpm) at four hours of life. Echocardiography revealed a 17 x 13 mm-sized tumour with relevant right ventricular outflow obstruction. The supraventricular tachycardia presented as undifferentiated narrow QRS complex tachycardia, most likely AV re-entry tachycardia. First, vagal manoeuvre was attempted, then 3 times administration of adenosine without termination of the supraventricular tachycardia. Therefore, a continuous amiodarone infusion was initiated. The infant was intubated, stabilised, and referred to our clinic. On day 13 of life, she had two episodes of ventricular tachycardia, resistant to electric and pharmacological cardioversion. After consent, we started sirolimus treatment with 0,4 mg/m2/dose, administered twice daily, with a target trough level of 10–12 ng/mL. After 2 days of administration, the level was 11.2 ng/mL (Figure). Two days later, the level was 31.9 ng/mL without changes in medication. We held sirolimus for several days, until the level drifted down to 7.9 ng/mL and restarted sirolimus at a

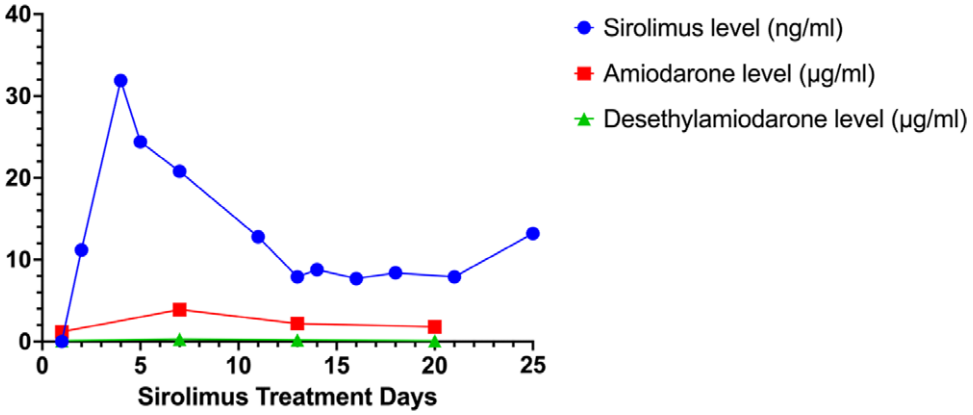

Figure 1. Amiodarone–sirolimus interaction.

reduced dose. Cardiac rhabdomyomas shrunk, and no further relevant arrhythmias were detected. Genetic testing confirmed a pathogenic de novo *TSC2* mutation. The patient continued sirolimus treatment until 3 months of age. Now at 1.5 years old, her cardiac status is stable; she reaches all developmental milestones while she is treated with vigabatrin for focal seizures and epileptic spasms.

Conclusions

Amiodarone and mTOR inhibitors, such as sirolimus, may interact significantly with increased risk of sirolimus toxicity, presumably due to inhibition of sirolimus metabolism by CYP3A4 inhibition by amiodarone. Treating physicians should monitor sirolimus levels and patients for sirolimus toxicity during concomitant therapy with amiodarone.

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Conflicts of interest. None.

Consent for publication. Written informed consent was obtained from the patient's parent.

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