

## Lengthening of QT Interval Caused by Fluconazole in a Newborn

Banu Aydin<sup>1\*</sup>, Dilek Dilli<sup>2</sup>, Ayşegül Zenciroğlu<sup>3</sup>, Nuran Uzunalic<sup>1</sup>, Nurullah Okumuş<sup>4</sup> and Mustafa Aydin<sup>1</sup>

<sup>1</sup>Fellow in Neonatology, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

<sup>2</sup>Neonatologist, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

<sup>3</sup>Associate Professor, Chief of Department of Neonatology, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

<sup>4</sup>Associate Professor, Vice Chief of Department of Neonatology, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

### Abstract

Fluconazole is a broadly used drug, especially in critically ill newborns hospitalized in neonatal intensive care units. The drug is safe and effective in both prophylaxis and treatment of fungal infections in newborns. In children, the most common side effects of fluconazole are associated with the gastrointestinal tract or skin. It can induce QT prolongation, which may lead to torsade de pointes and sudden death in adults, although rarely. We present lengthening of the QT interval in a newborn treated with fluconazole. To our knowledge, this is the first case of QT prolongation caused by fluconazole in this age group.

**Keywords:** Fluconazole; Newborn; Side effect; QT interval

### Introduction

The incidence of invasive fungal infections is gradually increasing among newborns hospitalized in neonatal intensive care units (NICU) [1]. Two populations of newborn infants are particularly vulnerable: the very low birth weight (VLBW) infants and newborn infants with severe neonatal digestive diseases, although fungal infections may be seen in any patients followed-up in NICU. *Candida albicans* is the species most often responsible for invasive candidiasis in the newborn. Fluconazole is being increasingly used to prevent and treat invasive candidiasis in newborns.

Fluconazole is a widely used bis-triazole antifungal agent. It functions mainly by inhibiting cytochrome P45014a-demethylase (P45014DM), which in turn, prevents the conversion of lanosterol to ergosterol in the sterol biosynthesis pathway. The drug appears to have a superior selectivity for fungus compared to human P-450-enzymes [2]. Fluconazole is well tolerated in adult patients, including those who are seriously ill. In adults, the most common experienced treatment-related side effects are gastrointestinal effects (nausea, abdominal pain, vomiting, diarrhea), headache, and skin rash. Rarely, it can induce QT prolongation, which may lead to torsade de pointes and sudden death [3,4]. In a study investigating safety and tolerability of fluconazole in 562 children (aged between 0-17 years), overall 58 (10.3%) children reported 80 treatment-related side effects. The most common side effects were associated with the gastrointestinal tract or skin. Self-limiting, treatment-related side effects affecting the liver and biliary system were reported only in three patients. Any cardiac side effects were not observed. It was concluded that safety profile of fluconazole in children showed excellent safety profile seen in adults [5].

In this article, we present a case of lengthening of the QT-interval in a newborn followed up in NICU and treated with fluconazole with suspect of nosocomial fungal infection. To our knowledge this is the first case report of QT prolongation in a newborn treated with fluconazole.

### Case Report

A-ten-day old female baby born at term as 2700 g of weight was brought to the outpatient clinics on her postnatal 10th day with complaints of feeding difficulty, irritability, and crying began two days ago. After initial evaluation, she was admitted to the NICU because of hypernatremic dehydration. On examination, she was agitated, her oral

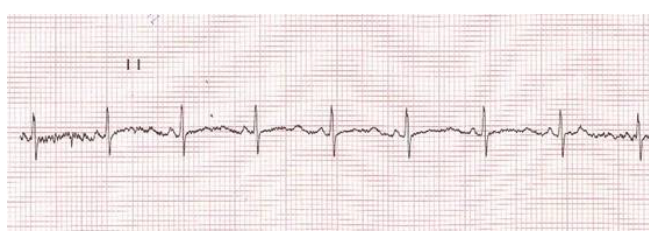
mucosa was dry, eyes were sunken, anterior fontanel was depressed, skin turgor and tonus were diminished. The baby's weight and vital signs were as follows: weight 2300 g (14.8% weight loss); fever 37.1°C; respiratory rate 52/min; heart rate 170/min; and blood pressure 73/20 mmHg. The other systems were normal. Whole blood count showed normal hematocrit (51.9%), hemoglobin (16.3 g/dl), and thrombocyte (208 000/mm<sup>3</sup>), but slight leucocytosis (17,600/mm<sup>3</sup>). Serum analyses showed abnormally high BUN: 116 mg/dl, creatinine: 2.7 mg/dl, uric acid: 12.1 mg/dl, sodium: 183.1 mEq/L, chloride: 146.5 mEq/L, and normal potassium (4.8 mEq/L) level. The other biochemical parameters were normal. Blood gas analysis showed mild respiratory acidosis. With suspect of sepsis, ampicillin and gentamicin were started empirically. With an appropriate fluid and electrolyte treatment, serum BUN, creatinine, sodium, and chloride levels were gradually diminished to 19 mg/dl, 0.62 mg/dl, 159 mEq/L, and 128 mEq/L respectively. Weight was increased to 2500 g. However, on 3rd day of hospitalization *Candida* casts were found in the urine specimen. After blood and urine cultures were taken, fluconazole therapy as 12 mg/kg loading, and then 6 mg/kg every 24 hours by intravenous route was planned. Two hours after the loading dose of fluconazole bradycardia (heart rate 60-70/min) developed. Electrocardiography showed that QT interval was 0.40 sec with a QTc (QT /  $\sqrt{R-R}$  sec) of 0.54 sec (Figure 1). In echocardiography, there was no cardiac defect except patent foramen ovale. Blood biochemical parameters which may be implicated for QT prolongation were within normal limits at this period. It was thought that fluconazole might cause this abnormality, and then the drug was stopped. Cardiac rhythm was normalized 24 hours after the cessation of the fluconazole treatment. Repeated electrocardiography revealed QT interval was 0.28 sec with a QTc of 0.38 sec (Figure 2). Antifungal treatment was not restarted as the patient was clinically stable and cultures were negative.

**\*Corresponding author:** Banu Aydin, Fellow in Neonatology, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey, Tel: 00 90 312 3056283; E-mail: [b\\_ay\\_yz@yahoo.com](mailto:b_ay_yz@yahoo.com)

Received March 16, 2012; Accepted July 10, 2012; Published July 13, 2012

**Citation:** Aydin B, Dilli D, Zenciroğlu A, Uzunalic N, Okumuş N, et al. (2012) Lengthening of QT Interval Caused by Fluconazole in a Newborn. J Clin Toxicol 2:132. doi:10.4172/2161-0495.1000132

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**Figure 1:** Electrocardiography of the patient performed during fluconazole treatment; note QT interval 0.44 sec (QTc = 0.55 sec) in DII.



**Figure 2:** Electrocardiography of the same patient performed after cessation of fluconazole treatment; note QT interval 0.28 sec (QTc = 0.38) in DII.

Antibiotic treatment was also stopped and the baby was discharged in good health on 8th day of hospitalization. Hearing test performed before discharge was normal.

## Discussion

Fungal-related morbidity and mortality is a major concern for most NICUs worldwide. Incidence rates are increasing and might be higher than reported due to the challenges associated with diagnosing fungal infections. Fluconazole is being increasingly used to prevent and treat invasive candidiasis in newborns.

It has been reported that it can be safely used in newborns and children without important side effects. Novelli and Holzel [5] stated that fluconazole was well tolerated by their study population of 562 children, many of whom were suffering from severe underlying disease such as HIV infection or hematological or oncological malignancies. They observed that the predominant reported side effects were gastrointestinal symptoms. In a recent research, Piper et al. [6] studied on 10 hospitalized infants <60 days old with suspected systemic fungal infection and they reported no adverse events were thought to be related to fluconazole therapy. In this paper we report a case of lengthening of the QT interval in a 10 days old newborn treated with fluconazole due to suspect of fungal infection.

The QTc interval represents the time in which ventricular myocytes are depolarized and repolarized. The interval is related to the heart rate and, therefore, is shortened in tachycardia and prolonged in bradycardia. Although not perfect, the Bazett formula ( $QTc = QT \text{ interval} / RR \text{ interval}$ ) is predominantly used to correct the QT interval for heart rate [4]. QTc intervals greater than 0.44 sec is considered pathologically prolonged. Like many diseases long QT syndrome has acquired and hereditary forms. The most common hereditary form is autosomal Romano-Ward syndrome, which is inherited in an autosomal dominant pattern. The other rare and malignant syndrome is Jervell and Lange-Nielsen syndrome, which is associated to deafness. Electrolyte disorders, myocarditis, and central nervous system diseases may lead to acquired QT prolongation [7]. Many drugs including proarrhythmic drugs, erythromycin, antihistaminics such as

terfenadine, domperidone, cisapride, and sevoflurane have shown to be associated with a prolonged QT interval [3,7].

Torsade de pointe is a polymorphic ventricular tachyarrhythmia associated with prolonged QT syndrome. Although the risk of torsade de pointes did not correlate in a linear fashion with prolongation of the QTc interval, but an interval beyond 500 msec was considered to be a significant risk factor [4]. Fluconazole, a commonly used azole antifungal drug can also induce QT prolongation, which may lead to torsade de pointes and sudden death. Tacken et al. reported [3] the occurrence of torsade de pointes induced by the combination of perioperative fluconazole administration and sevoflurane anesthesia in a patient with 'long QT syndrome' scheduled for resection of a sacral abscess. They reported that eight minutes following uneventful induction of anesthesia torsade de pointes occurred, terminated by a counter shock and concomitant administration of fluconazole might have further predisposed the patient to the development of torsade de pointes. Similarly, Pham et al. [4] reported that they observed prolongation of the QTc interval and torsade de pointes caused by fluconazole in a 33-year-old woman admitted to the intensive care unit because of *Candida albicans* pneumonia. They speculated that fluconazole was the highly probable cause of the development of torsade de pointes in their patient. Recently, Han et al. [8] investigated the arrhythmogenic side effects of fluconazole. They studied the effect of fluconazole on human ether-a-go-go-related gene (hERG) K (+) channels (wild type, Y652A and F656C) expressed in human embryonic kidney (HEK293) cells. They found that fluconazole inhibited wild type hERG currents in a concentration-dependent manner, with a half-maximum block concentration (IC (50)) of  $48.2 \pm 9.4 \mu\text{M}$  without changing other channel kinetics (activation and steady-state inactivation) of hERG channel. They concluded that fluconazole might cause acquired long QT syndrome via a direct inhibition of hERG current and by disrupting hERG protein trafficking, and the mutations Y652 and F656 might be obligatory determinants in inhibition of hERG current for fluconazole. In the present case, we also observed that fluconazole led to QT prolongation to 0.40 sec (QTc of 0.54 sec), but not torsade de pointes. One day after cessation of fluconazole treatment it was observed that QT duration was decreased to 0.28 sec (QTc 0.38) without another treatment.

Acquired prolongation of QTc interval is primarily caused by drugs, especially when used in combination therapy. QT prolongation has been described in patients using combinations of drugs, including fluconazole [9], as well as in patients with baseline cardiac abnormalities who are receiving fluconazole. It has been speculated that when used in combination the drugs that inhibit the function of cytochrome P450 isoenzymes, especially in a patient with impaired renal function, the concentration of fluconazole can rise above therapeutic level and resulted QT prolongation [4]. Our patient had renal impairment on admission. However, serum concentration of fluconazole to support this hypothesis was not determined. The patient had not received any drugs which possibly affect QT interval. Blood biochemical parameters which may be implicated for QT prolongation were within normal limits at this period.

It was previously established that the pharmacokinetic properties of fluconazole peak plasma concentrations (Cmax) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20–50 hours) after oral administration [10]. In the presented case, QT prolongation was observed 2 hours after the fluconazole infusion and QT interval returned to normal limits 24 hours after the cessation of the drug. This

condition has suggested that QT prolongation might be caused by fluconazole.

To our knowledge, prolongation of the QTc interval caused by fluconazole monotherapy has not been previously reported in newborns, although there are some reports in adults [4,11]. Finally, fluconazole is a widely used drug, especially in critically ill newborns. From the case history presented here, we want to emphasize that clinicians should be aware that fluconazole monotherapy, especially when baseline QTc interval is prolonged and perhaps when renal function is impaired, can result in QTc interval prolongation. Monitoring of the heart rhythm and associated QTc interval is advisable, and determination of fluconazole serum concentration may be a useful adjunct in preventing this potentially lethal complication in patients with several risk factors for prolongation of QTc interval.

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