NEONATAL RECURRENT PROLONGED HYPOTHERMIA ASSOCIATED WITH MATERNAL MIRTAZAPINE TREATMENT DURING PREGNANCY

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ABSTRACT

We present a case of recurrent hypothermia in concordant monozygotic twins born to a mirtazapine treated mother. The twins were born at 35 weeks gestation at birth weights of 2426 g and 2355 g. Both twins presented with recurrent hypothermia continuing until day 10 of life. Possible etiologies of hypothermia were excluded. The degree of prematurity and the weight of the twins were not consistent with prolonged thermal instability. The twins' mother was treated with mirtazapine during the entire pregnancy. Due to its serotonin and alpha 2 receptors antagonism mirtazapine is known to influence thermoregulation in adult humans and other mammals. We suggest that maternal mirtazapine treatment during pregnancy was associated with recurrent hypothermia in both identical twins.

Key words: *Mirtazapine, hypothermia, newborn*

Mirtazapine is a unique antidepressant tetracyclic agent, unrelated to other known classes of antidepressants. The drug exhibits both noradrenergic and serotoninergic activity by blocking alpha-2 receptors and antagonizing the serotonin receptors 5-hydroxytryptamine 2 (5-HT2) and 5-hydroxytryptamine 3 (5HT3). It is also an antagonist of the H-1 histamine receptor and a moderate peripheral alpha-1 adrenergic and muscarine antagonist.[1] Because mirtazapine has a low molecular weight (265), transplacental transfer to the fetus in measurable amounts is anticipated.[2] Common side effects of mirtazapine include drowsiness, dry mouth, increased appetite, weight gain and dizziness. Mirtazapine has been shown to affect thermoregulation in animals and in humans.[3-8]

The aim of the present report is to describe the possible association of recurrent prolonged hypothermia in identical twins with antenatal exposure to mirtazapine.

Case Report

A 34 year-old gravida-4, para-3 woman was treated for the entire duration of her pregnancy with mirtazapine. She received a daily dose of 30 mg for an anxiety disorder. The current pregnancy was a spontaneous twin pregnancy and its course was uneventful except for mild hypertension that did not require treatment. Cesarean section was performed at 35 weeks due to cord prolapse of the second twin. The birth weight of twin 1 was 2426 grams (percentile 78% by Usher curves) and his Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. Physical examination was normal. Twin 2, whose cord had prolapsed, was born at a birth weight of 2355 grams (percentile 70% by Usher curves). His Apgar scores were 5 and 9 at 1 and 5 minutes, respectively. On initial physical examination at the age of four hours, mild hypotonicity and poor sucking were noted, but physical and neurological examinations at 24 hours were normal. No congenital malformations were identified in either twin. The twins where concordant by weight, identical by sex (both males) and by blood type. According to the protocol in our nursery for preterm and low birth weight infants, the twins where initially placed in incubators set at a standard temperature determined by birth-weight and postnatal age. The mother elected not to breast-feed. After 24 hours during which normal body temperature was

maintained, the twins where transferred to a warmed bassinet for an additional 24 hours, during which body temperature was maintained within the normal range. On the third day of life, the twins where moved to regular cots. After 14 hours without warming, the body temperature measured per rectum (PR) of both twins was 36.1 C° and physical examination was normal. The mild hypothermia of both twins was attributed to prematurity and after 8 hours in a warmed bassinet, during which normal body temperature was maintained, the twins were transferred to regular cots. Within a few hours the body temperature dropped again to 36.1 C° (PR) in twin 1 and to 36.0 C° (PR) in twin 2. Physical examination was otherwise normal and warming of both twins was resumed. Following discontinuation of heating on day six of life, the body temperature dropped to 35.8 C° (PR) on repeated measures for both twins. Twin 1 was alert and in good general condition but twin 2 showed delayed reactivity and mild hypotonicity. Both twins were re-warmed again and evaluated for sepsis. The evaluation included complete blood count, C- reactive protein and blood culture for both twins and also cerebrospinal fluid and urine cultures for twin 2. Additional laboratory evaluation included glucose, electrolytes, renal and liver functions and thyroid function. Both twins were started on antibiotic therapy (ampicillin and gentamycin) following initial evaluation.

All laboratory tests were within normal ranges and all cultures were sterile. Head ultrasound was normal for twin 2. Reactivity and muscle tone of twin 2 normalized 24 hours after performing the sepsis work-up. Thermal instability and borderline hypothermia of 36.0 C° in both twins continued until their tenth day of life and was normal from then on. Both twins did not show any sign of a withdrawal syndrome and Finnegan scores for assessment of signs of drug withdrawal were normal. Follow-up at the age of 4 months showed normal growth and development of both twins.

DISCUSSION

We present the case of near-term twin newborns with abnormal thermoregulation presenting as repeated episodes of mild to moderate hypothermia during the first 10 days of life. The twins' mother was treated for anxiety disorder with mirtazapine throughout her pregnancy.

The World Health Organization classifies a newborn core body temperature of 36.0 to 36.4 C° as mild hypothermia, 32 to 35.9 C° as moderate hypothermia and lower than 32 C° as severe hypothermia.[9] Currently there is no accepted formal definition of 'normal' temperatures for preterm infants, and methods and accuracy of temperature measurement are controversial.[10,11]

Hypothermia in newborns has many etiologies. The high ratio of skin surface area to body weight, limited brown fat tissue and decreased subcutaneous fat predispose preterm infants to hypothermia. Prolonged hypothermia is extremely unusual in the appropriate for gestational age late-preterm infant that is kept in a protected environment. Any hypothermic infant should be initially evaluated for sepsis, as hypothermia is a common symptom of sepsis in the newborn. Sepsis was excluded in both twins.

Other causes of hypothermia such as endocrinopathy or that resulting from cardiac failure were improbable in this case since the twins were in general good condition, did not exhibit physical findings compatible with these disorders, had no signs of malnutrition, had normal thyroid function and did not have episodes of hypoglycemia. Meningitis was ruled out by lumbar puncture for twin 2 and considered unlikely for twin 1, who did not have symptoms compatible with meningitis neither at the time of hypothermia, nor throughout his entire hospital course. There were no clinical features of hypoxic ischemic encephalopathy. Head ultrasound was normal and there were no signs of any other central nervous etiology for hypothermia such as encephalitis, intraventricular hemorrhage, tumors or congenital malformations. No drug other than mirtazapine was taken by the mother or given to the twins. There was no exposure to cold conditions and no dermal disease. Withdrawal from mirtazapine does not seem to be the cause of hypothermia because no other signs of withdrawal were present. Although pediatric half-life has not been measured[1], the mean drug half-life of mirtazapine is 20-40 hours with recorded half-lives of up to 65 hours. The long drug half-life supports the possibility of an adverse drug effect, as complete elimination of the drug may not have

been achieved at the time of cessation of hypothermia.

The likelihood that mirtazapine induced hypothermia in the twins is probable, as estimated by the Naranjo adverse drug reaction scale.[12] Abnormal thermoregulation in newborns of mirtazapine-treated women has not been described to our knowledge. Pregnancy outcome following exposure to mirtazapine was assessed by Djulus et al.[1] Mirtazapine does not appear to increase the risk of major congenital malformations but may increase the rates of preterm birth and of spontaneous abortions.[1] Retz et al[3] reported a case of mirtazapine intoxication complicated by hypothermia; but, their patient was exposed to a cold environment, which was a possible etiology for hypothermia.

Thermoregulation is a complex process involving many components. Important components of this process include: core body temperature, peripheral vasculature, the central nervous system and neuronal and endocrine messaging systems. Regulation of body temperature by the central nervous system is not completely understood. Animal studies have demonstrated the importance of serotonergic neurotransmission in the thermoregulation of mammalian body temperature, but their results are inconsistent.[4,5] Pawlyk et al[4] examined the effects of mirtazapine on thermoregulation in rats and showed that mirtazapine is a potent functional antagonist of the 5HT2a receptor. Mirtazapine induced a dose dependent decrease in core body temperature but interestingly, caused an increase in tail skin temperature. Animal data implies that serotonin 5HT2a receptors take part in thermoregulation, but this may not necessarily be the case in humans.

Clinical reports suggest that mirtazapine may be an effective treatment of vasomotor symptoms in menopausal women.[6-8] While blockage of 5HT2a receptors by mirtazapine is possible in humans, the precise mechanism by which mirtazapine affects human thermoregulation has not been sufficiently studied.

In summary, we have presented identical twins with prolonged hypothermia associated with maternal mirtazapine treatment. This is the first description of this phenomenon in newborns of a mirtazapine-treated woman. Additional reports are needed to confirm the association of prenatal exposure to mirtazapine with neonatal hypothermia.

REFERENCES

1. Djulus J, Koren G, Einarson TR, et al. Exposure to mirtazapine during pregnancy: a prospective, comparative study of birth outcomes. J Clin Psychiatry 2006;67:1280-1284.
2. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th, Ed. 2005, pp:1090-1091. Lippincot Williams & Wilkins, Philadelphia, USA
3. Retz W, Maier S, Maris F, Rosler M. Non-fatal mirtazapine overdose. Int Clin Psychopharmacol 1998;13:277-9.
4. Pawlyk AC, Cosmi S, Alfinito PD, Maswood N, Deecher DC. Effects of the 5-HT2A antagonist mirtazapine in rat models of thermoregulation. Brain Res 2006;1123:135-44.
5. Sipe K, Leventhal L, Burroughs K, Cosmi S, Johnston GH, Deecher DC. Serotonin 2A receptors modulate tail-skin temperature in two rodent models of estrogen deficiency-related thermoregulatory dysfunction. Brain Res 2004;1028:191-202.
6. Buecking A, Vandeleur CL, Khazaal Y, Zullino DF. Mirtazapine in drug-induced excessive sweating. Eur J Clin Pharmacol 2005;61:543-4.
7. Perez DG, Loprinzi CL, Barton DL, et al. Pilot evaluation of mirtazapine for the treatment of hot flushes. J Support Oncol 2004;2:50-6.
8. Waldinger MD, Berendsen HH, Schweitzer DH. Treatment of hot flushes with mirtazapine: four case reports. Maturitas 2000;36:165-8.
9. Thermal protection of the newborn: a practical guide. The World Health Organization publications, 1997.
10. Smith LS. Temperature monitoring in newborns: A comparison of thermometry and measurement sites. J Neonat Nurs 2004;10:157-165.
11. Bailey J, Rose P. Temperature measurement in the preterm infant: A literature review. J Neonat Nurs 2000;6:28-32.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-45.