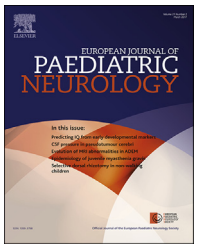
ELSEVIER

Official Journal of the European Paediatric Neurology Society



Review article

Neonatal venlafaxine discontinuation syndrome: A mini-review

*Jonathon Holland, Richard Brown**

Peterborough City Hospital, Bretton Gate, Peterborough, Cambridgeshire, PE3 9GZ, United Kingdom

ARTICLE INFO

Article history:
Received 21 June 2016
Received in revised form
20 November 2016
Accepted 20 November 2016

Keywords:
Venlafaxine
Withdrawal
Neonate
Abstinence
Discontinuation
Encephalopathy

ABSTRACT

During pregnancy, the developing fetal brain may be exposed to a range of psychotropic medications. The serotonin-noradrenergic reuptake inhibitor venlafaxine is one such drug, when used as a maternal antidepressant. Here we review the discontinuation phenomenon that may follow in exposed neonates following birth.

Adults who abruptly stop taking venlafaxine can experience withdrawal symptoms. Venlafaxine and its metabolites cross the placenta and so the newborn can be exposed to this risk, as well as potential toxicity. Several case reports document features of encephalopathy following birth in exposed neonates. It is suggested that a possible combination of partial toxicity together with withdrawal may lead to these symptoms – a discontinuation syndrome. The underlying neurobiology is not yet established.

Common symptoms and signs seen in affected neonates include poor feeding, jitteriness, respiratory distress and myoclonic seizure-like activity. Onset is typically between birth and day 4 of life with resolution by 2–21 days of life. Electroencephalography does not necessarily correlate with clinical seizures, or response to anticonvulsants. In limited follow-up data, no long-term consequences of this discontinuation syndrome are reported.

We suggest where it is not possible for mothers to be switched from venlafaxine to other antidepressant drugs, that their infants are observed closely for 2–4 days following delivery. In symptomatic neonates, following exclusion of other causes, supportive care including breastfeeding may be sufficient for management. Clinicians should be vigilant to venlafaxine discontinuation as a cause for encephalopathy or paroxysmal episodes in exposed neonates.

Contents

Abbreviations: SNRI, serotonin-noradrenergic reuptake inhibitor; SSRI, serotonin-selective reuptake inhibitor; EEG, Electroencephalogram.

* *Corresponding author*. Department of Paediatrics, Peterborough City Hospital, Bretton Gate, Peterborough, PE3 9GZ, United Kingdom.
E-mail addresses: Jonathon.holland@nhs.net (J. Holland), Richard.Brown@pbh-tr.nhs.uk (R. Brown).

http://dx.doi.org/10.1016/j.ejpn.2016.11.003

1. Introduction/background

Following birth, neonates may withdraw from many substances to which they were exposed *in-utero*. Neonatal abstinence syndrome associated with opiate withdrawal is well described and it is recognised that exposure to medications such as benzodiazepines can lead to withdrawal.[1] As new pharmaceuticals are developed and used in pregnancy it is important that such side-effects are characterised. In this mini-review we summarise current knowledge of the neonatal venlafaxine discontinuation syndrome.

Venlafaxine was first marketed in 1993 as an adult antidepressant. At low doses it has similar effects to SSRIs, modulating serotonergic neurotransmission, whilst at higher doses it acts as an SNRI, additionally affecting noradrenergic transmission.[2]

In adults, overdose is recognised to present with seizures and cardiovascular disturbances, as well as serotonin toxicity syndrome.[3] A withdrawal state is recognised; this varies in severity and features a wide range of symptoms.[4]

Fetal exposure to venlafaxine can result in several adverse neonatal effects, including respiratory distress, low blood sugar and seizures. Clinicians treating depression in pregnant women taking venlafaxine therefore have to take in to consideration the benefits to the mother's mental health, versus the potential risks to the fetus.[5]

Here we will discuss the discontinuation phenomenon that has been observed in the newborn infants of some mothers who were using venlafaxine during pregnancy, in order to help assist such clinical decision-making, as well to increase awareness amongst healthcare providers.

2. Method

A PubMed search was performed using the terms "venlafaxine" AND "neonate" returning 39 results. 8 relevant articles were identified featuring reports on 13 neonates who developed features of withdrawal. One additional newborn displaying features of withdrawal known to the authors was included.[6] Selected further references were also examined.

3. Discussion

The first known published case report of an infant experiencing a probable venlafaxine withdrawal syndrome dates to 2003[7]; characteristics of this and 13 further neonates to date are described in Table 1.

3.1. *Presenting characteristics*

Three articles[7,9,11] describe neonates exhibiting concerning features at the time of and shortly after birth. One describes an infant developing hypoglycaemia and tremor,[7] and another reports an infant requiring resuscitation at birth.[9] In the third, from 7 newborns exposed, 3 presented with respiratory distress (one which required resuscitation) and 1 with tachypnoea from birth.[11]

Amongst the other case reports, symptom onset occurred later, from age 12 h[11] to day 4 of life.[13] Frequently these included 'jittery' movements,[7,8,11] poor feeding/sucking,[7,8,12] tachypnoea[6,8,11,12] and myoclonic seizures.[6,9,12–14] Commonly reported morphology included extensor limb posturing[9,12] and (multifocal) myoclonic seizures.[6,9,13,14]

In the 6 newborns with reported seizures, 3 had normal EEGs. The other 3 had abnormal EEGs, with no consistent significant features between them. EEG changes did not necessarily correlate to epileptiform activity. Furthermore, in 2 infants who were treated with phenobarbitone, although seizures resolved clinically, EEG activity remained abnormal.[13,14] One infant was given phenytoin, causing normalisation of EEG but also hypotonia and diminished reflexes; it was therefore stopped and seizures returned.[13]

In the 5 affected newborns studied by Boucher et al., it was noted that the neonate whose mother was taking the highest venlafaxine dose had "the most severe and longer lasting clinical signs".[11] This newborn also had the lowest gestational age. However, amongst all other reported cases, it is difficult to see a correlation between maternal dose or gestational age and symptoms, with many confounding factors.

All neonates were screened for other causes for their symptoms such as sepsis. Electrolyte abnormalities[14] and hypoglycaemia[7] were identified in some cases; however, clinical features persisted after correction of these potential aetiologies.

3.2. *Establishing withdrawal versus toxicity*

The symptoms displayed by newborns exposed to venlafaxine prior to delivery are variously described using terms such as withdrawal, abstinence and discontinuation. Some authors highlight that, alternatively, venlafaxine toxicity may be causative. This is possible given that venlafaxine and its metabolites are suggested to cross the placenta and have an