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Visual evoked potential latencies of three-year-old children prenatally exposed to buprenorphine or methadone compared with non-opioid exposed children: The results of a longitudinal study

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ABSTRACT

This study compared the latency of pattern reversal visual evoked potentials (VEP) of 36-month old children exposed to opioid pharmacotherapy in utero to that of a group of non-exposed children. Pregnant women were enrolled as part of an open-label non-randomised flexible dosing longitudinal study. Participants were 21 children whose mothers were treated with buprenorphine- (n = 11) or methadone-pharmacotherapy (n = 10) during pregnancy, and 15 children not exposed to opioids in pregnancy. One-way between groups analyses of variance (ANOVA) were conducted to test the statistical significance of differences between the mean latencies of the peak response to two different sized checkerboard patterns (48′ and 69′ of retinal arc). Standard multiple regression analyses were conducted to determine whether there was a significant relationship between group status and VEP latencies after adjusting for the effect of covariates. VEP latencies ranged from 98 to 112 milliseconds (ms) for checks of 48′ arc, and from 95 to 113 ms for checks of 69′ arc. Latencies were comparable across groups. After adjusting for covariates children prenatally exposed to methadone or buprenorphine did not differ significantly from non-opioid exposed children in their responses to either check size. Nor were there any significant differences in VEP latencies between children prenatally exposed to methadone and children prenatally exposed to buprenorphine. Head circumference (HC) was significantly associated with P100 latencies for both check sizes. Data from this controlled, non-randomised study suggest that neither buprenorphine nor methadone appear to have any long-term effects on visual maturity assessed at 36 months of age.

1. Introduction

Substance misuse during pregnancy results in poorer maternal and foetal outcomes compared with non-exposed populations (Adams et al., 1989; Chang et al., 1992; Farid et al., 2008; Kaltenbach et al., 1998). In Australia, approximately 1/100 women use illicit substances during pregnancy, and up to 5% of infants admitted to neonatal intensive care units are prenatally exposed to at least one illicit substance (Abdel-Latif et al., 2007; Kennare et al., 2005; Oei and Kei, 2007).

Women who use illicit opioids in pregnancy experience a high rate of obstetric complications which may result from the drug itself, or from concomitant use of other illicit substances, poor maternal nutrition, an unstable lifestyle, and poor attendance or non-compliance with antenatal care (Adams et al., 1989; Australian Drug Foundation, Heroin, Australian Drug Foundation, 2005; Kaltenbach et al., 1998; Kennare et al., 2005; Morse et al., 1989; Sobrian et al., 1989). Exposed infants have increased risk of prematurity, lower Apgar scores, lower birth weight (and being small for gestational age), neurobehavioural problems and greater risk of sudden infant death syndrome (SIDS), when compared with non-exposed infants (Berlin et al., 1998; Chang et al., 1992; Kandall et al., 1976; Koren et al., 2005; Laken et al., 1997; Robins and Mills, 1993; Sobrian et al., 1989). Infants exposed to opioids in pregnancy are also at high risk of developing neonatal abstinence syndrome (NAS) (Finnegan, 1990; Finnegan and Kandall, 1997; Kaltenbach, 1994; Kandall et al., 1977).

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1.1. Methadone

In Australia, methadone pharmacotherapy is the first line treatment for pregnant women with heroin-dependence (Dunlop et al., 2003; Lintzeris et al., 2006) and has a range of benefits for mothers (Chang et al., 1992; Dunlop et al., 2003; Lintzeris et al., 2006; Wilson, 1989) and infants (Kandall et al., 1976; Lifschitz et al., 1983; Wilson, 1989; Wilson et al., 1981; Wilson et al., 1979). Whilst treatment with methadone during pregnancy results in fewer complications for both mother and infant when compared with the use of illicit opiates, it is associated with high rates of NAS (60–80% of methadone treated pregnancies) (Finnegan and Kandall, 1997; Lundgren et al., 2007).

1.2. Buprenorphine

Buprenorphine, a synthetic opioid, is now widely used in the treatment of non-pregnant opiate-dependent individuals. A number of early observational studies have supported its safety and efficacy during pregnancy and the neonatal period (see (Johnson et al., 2003) for a review). However, these studies have been limited by low subject numbers and lack comparison with existing treatments or non-exposed controls (Fischer et al., 2000; Johnson et al., 2001; Kayemba-Kay's and Laclyde's, 2003; Lejeune et al., 2006). Results from larger, more recent studies indicate better neonatal outcomes may be expected for infants prenatally exposed to buprenorphine when compared with those exposed to methadone, including greater gestational age at birth, increased birth growth measurements, decreased severity of NAS and duration of NAS treatment, and shorter hospital stays for infants (Brogly et al., 2014; Czerkes, 2010; Ebner et al., 2007; Fischer et al., 2006; Jones et al., 2005; Jones et al., 2010; Kakko et al., 2008; Lejeune et al., 2006). Research to date indicates that maternal treatment with buprenorphine may offer advantages over methadone pharmacotherapy during pregnancy and the neonatal period in terms of low transplacental transfer and less exposure to active medication through breast milk (Gordon et al., 2010; Johnson et al., 2003; Nanovskaya et al., 2002).

Despite these positive outcomes for pregnant women and neonates exposed to buprenorphine in utero, methadone remains the gold standard of care for the treatment for pregnant women with opioid-dependence (Center for Substance Abuse Treatment, 2004; Lintzeris et al., 2006). This is because the safety, efficacy and effectiveness of buprenorphine throughout pregnancy and the neonatal period has not yet been definitively established, and because there is a paucity of data regarding longer-term childhood outcomes (Lintzeris et al., 2006).

1.3. Child development

Whilst some researchers have reported adverse outcomes for children prenatally exposed to either illicit heroin use or methadone pharmacotherapy (van Baar and de Graaff, 1994), others have reported no longer-term developmental problems (Hunt et al., 2008; Kaltenbach and Finnegan, 1987; Messinger et al., 2004; Wilson, 1989). There is a paucity of research examining children's cognitive development longitudinally, and many studies have not compared outcomes with those of non-exposed infants, have had small samples, or poor follow-up rates. Previous studies examining the longer-term neurodevelopment of children prenatally exposed to buprenorphine have been limited to case reports (Schindler et al., 2003), retrospective reviews (Kayemba-Kay's and Laclyde's, 2003) and prospective studies with small numbers (Kahila et al., 2007; Salo et al., 2009; Sandtorv et al., 2009).

In the only controlled study, Salo et al. (2009) compared the development of 21 children prenatally exposed to recreational use of buprenorphine and 13 non-exposed children. At three years of age, children prenatally exposed to buprenorphine achieved significantly poorer standardised scores on the Cognitive and Language Scales of the Bayley Scales of Infant Development — Third Edition (BSID-III), compared with the non-exposed children. After adjusting for covariates (including birth weight and height, gestational age, maternal age, socioeconomic status and number of foster placements), only the Language Scale scores remained associated with substance-exposure. It is important to note that the majority of buprenorphine-exposed children were also prenatally exposed to other illicit substances which may have contributed to the poorer outcomes (Salo et al., 2009).

1.4. Visual evoked potentials

Visual Evoked Potentials (VEPs) measure the changes in brain wave electrical activity in response to a visual stimulus. The activity is recorded non-invasively from the scalp in the region of the visual cortex and is processed by data averaging time locked to the stimulus so as to extract the stimulus specific responses. VEPs test the integrity of the visual pathway from the retina to the occipital cortex and provide information about neural maturity (Cibis and Fitzgerald, 1993). They reflect brain development in terms of axon and dendrite growth, synapse formation and degree of myelination (Pryds et al., 1989; Scher et al., 1998).

VEP latency provides a measure of the speed of processing from the visual stimulus to the peak of neuronal depolarisation in the primary visual cortex (Algarin et al., 2003; Aso et al., 1988; Hansen et al., 1993; Madrid and Crognale, 2000; Pinto et al., 1986; Skarf, 1989). A decrease in latency to the first major positive component (P1) elicited through VEP is a reliable index of visual maturation, predominantly associated with myelination of the optic nerve (Aso, 1988).

Our group has previously compared the latency of pattern reversal VEP for infants prenatally exposed to buprenorphine ($n = 30$) or methadone ($n = 22$) with that of a comparison group of non-exposed infants ($n = 33$) (Whitham et al., 2010). At four months of age P100 latencies of infants prenatally exposed to buprenorphine did not differ significantly from those of non-exposed infants. In contrast, infants prenatally exposed to methadone had significantly prolonged P100 latencies when compared with both comparison infants and those exposed to buprenorphine. These relationships were evident for P100 latencies in response to checks of 48 and 69 min (′) of retinal arc. After controlling for covariates, including corrected age at testing, the effect of prenatal exposure to methadone was no longer a significant predictor of P100 latencies in response to checks of 69' of arc. Maternal self-reported used of marijuana during pregnancy remained a significant predictor of delayed P100 latencies in response to both check sizes (Whitham et al., 2010).

Previous research has found delays in visual functioning and abnormalities in ophthalmic outcomes for children prenatally exposed to methadone and illicit opiates (Hamilton et al., 2010; Lodge et al., 1975; McCulloch et al., 2007; McGlone et al., 2008; Mulvihill et al., 2007). McGlone and colleagues (McGlone et al., 2014) have recently presented the results of comprehensive visual assessment at six months of age for 81 infants prenatally exposed to methadone and 26 non-exposed comparison infants. Visual disturbances, including strabismus, reduced visual acuity and nystagmus, were evident in 40% of the substance-exposed infants, with 70% of substance-exposed infants having abnormal VEP responses (delayed peak responses or small amplitudes). Whilst the majority of methadone-exposed infants were also exposed to other illicit drugs or excess alcohol in utero, the authors found no association between visual outcome and pattern of prenatal substance exposure or history of NAS. The specific effect of exposure to methadone alone could not be established, as data were too few. The authors concluded that prenatal drug exposure might alter the functioning of visual pathways and/or cerebral sources of VEP, and proposed a cause-effect relationship between in utero drug exposure and infant visual anomalies (McGlone et al., 2014).

Additionally, Spiteri Cornish et al. (2013) have documented increased incidence of persistent ophthalmic morbidities (strabismus, nystagmus, poorer visual acuity and lack of binocularity) in children prenatally exposed to heroin, methadone, cocaine, amphetamines, or