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Pharmacologic Therapy for Neonatal Abstinence Syndrome

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ABSTRACT

A pregnant woman who happens on a continuous exposure to various therapeutic agents during her gestation period may give birth to a neonate suffering from Neonatal Syndrome. The most common cause of NAS are opioids such as heroin, codeine and morphine and is commonly termed as opioid withdrawal syndrome but also other legally or illegally sold substances over the counter can contribute to this syndrome. Infants also develop some kind of addition in the womb when exposed to some antidepressants such as barbiturates and benzodiazepine. There are two kinds of NAS that exist, prenatal NAS which is as a result of the termination of medication being used with a pregnant mother and postnatal NAS which occurs as a result of the termination of drugs directly to the infant. The most frequently occurring syndrome consists of tremor, insomnia, perspiration, Common syndrome according to the frequency includes tremor, high-pitched sneezing sound, increased muscle tone, regurgitation and emesis, loose stools, s, excoriation, mottling, nasal congestion low-grade fever, and tachypnea. Opioid withdrawal symptoms can be a reflection of other symptoms of other conditions in a new-born, such as infections, hypoglycaemia, hypocalcaemia, hypothyroidism, and brain complications (eg., cerebral palsy). The need and time frame of treatment is reduced by breastfeeding. All NAS babies need to be followed up regularly. Not all infants will require treatment with pharmacotherapy, but all should receive non-pharmacologic interventions.

Keywords: Neonatal abstinence syndrome; Nonpharmacological management; Methadone; Morphine; Opioids; Pharmacological management; Phenobarbital; Protocol.

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INTRODUCTION

Neonatal abstinence syndrome (NAS) is described as a sequence of symptoms typically witnessed in the new-born of a mother who has taken opioids and other drugs for a long duration period in the antepartum period (Jansson et al., 2012). Withdrawal symptoms tend to occur in new-borns who no longer receive opioids that had been systemically delivered via the placenta immediately after parturition. The implications of NAS usually appear with an onset of symptoms on the fifth day of life depending on the type of medication received by the mother and lasting up to six months of age (Shearer et al., 2018).

ETIOLOGY

There are two major kinds of NAS. The prenatal NAS is the most widely known and occurs commonly in antepartum use of substances. Withdrawal symptoms appear in the neonate once the placental access to the drug is no longer at its disposal. Postnatal NAS develops in sudden termination of analgesics, such as Fentanyl or morphine, occurs usually after one being exposed to for a very long time after surgery for management of pain to cause sedation (Nancy et al., 2014).

PATHOPHYSIOLOGY OF NAS

The pathophysiological mechanism that results in opioid withdrawal syndrome in neonates is an idiopathic case. Numerous factors can affect the build-up of opioids in the fetus. Opiate drugs have low molecular weights, are hydrophilic in nature, and are lipophilic substances; hence, they easily pass across the placenta membrane to the fetus. There is a direct relationship between opioid transportation across the placenta and gestation. Transportation of opioids increases with an increase in gestation (Nanovskaya et al., 2008). Opioid deficiency also alters the functioning of the autonomic and peripheral nervous systems, as well as the gastrointestinal system. Opioid deficits cause increased release of a variety of neurotransmitters, such as acetylcholine, during the phase of withdrawal (Passo et al., 2011). Neonates whose mothers used an SSRI or SNRI may

result in profuse production of serotonin and noradrenaline as withdrawal symptoms. Neonatal withdrawal from TCA is a cholinergic rebound phenomenon. There is a high possibility in increasing production of amino acid as a result of withdrawing benzodiazepine (Sanj et al., 2005).

MANAGEMENT

The core objective as regards to the management of NAS is to encourage normal growth development. Primary concerns regarding the management of the NAS is to promote normal growth development and to avert or reduce negative effects such as convulsions and discomfort in the new-born and impaired maternal bonding (Kraft et al., 2016).

NONPHARMACOLOGIC THERAPY

All children at risk of NAS need to be taken care through a non-chemotherapeutic approach aimed at providing a peaceful and calming atmosphere while avoiding excessive stimulation of environment. Frequent high-calorie foods reduce hunger and promote growth (Jansson et al., 2009). Non-nutritious absorption helps reduce stress in the child and has irregular and irregular movements (Velez et al., 2008).

PHARMACOLOGIC THERAPY

Pharmacotherapy is an indispensable part of management when nonpharmacological care is inadequate to relieve the complications associated with neonatal abstinence syndrome. About 20% to 40% of children with the syndrome do respond to non-pharmacological remedies and don't require medication (Kocherlakota, P., 2014). The core objective weight loss of pharmacologic therapy is to relieve moderate-to-severe signs such as seizures, fever, and weight loss (Hudak et al., 2012). AAP guidelines based on current evidence and practice in the United States demonstrates oral morphine and methadone as first-line therapies. (Jansson et al.2009). Clonidine and phenobarbital concentrations can be closely checked and both play a vital role in reducing the duration of therapy as well as cut back the use of higher doses of morphine or methadone (Kuschel, C., 2007; Agthe et al.,2009). Delays in pharmacologic treatment intervention are linked to higher morbidity and longer hospitalization periods. (Finnegan et al., 1992)

LONG TERM EFFECT

Evaluation of the long-term effect of NAS has been a major problem due to the scarcity of research opportunities. Symptoms often begin within one to three days after birth but may take up to a week to appear. Newborns with NAS may exhibit abnormal behaviors up to 6 to 9 months of age (Behnke et al., 2013). Adverse neurodevelopmental syndromes have been observed in infants and children exposed to opioids *in utero*. There is relatively scanty information on long-term neurodevelopmental implications. This is especially due to scanty studies that are not in a position to distinguish between the effects of *in utero* exposures and postnatal treatments with environmental variables influences. In general, opioid-exposed children are at high risk to have attention deficit disorders, disruptive behavior, and the need for comprehensive psychiatric referrals (Ornoy et al., 2010)

BREAST FEEDING

American Academy of Paediatrics in 2001 rejected any the restrictions on lactating mothers on any dosage of methadone (American Academy et al.2001). Breastfeeding may reduce the incidence of NAS (Welle-Strand et al., 2013).

OPIOIDS

Morphine and Methadone:

The two major opioids that have found relevance in practice are oral morphine and methadone. Morphine is the primary opioid used in most of the centers, with methadone being used in 10–20% of hospitals (Patrick et al., 2014). Normally the doses start from 0.2 mg/kg/day. Some treatment regimens require a loading dose of 0.1 mg/kg (Lainwala et al., 2005).

Buprenorphine:

Buprenorphine a partial opioid agonist is a new addition in NAS treatment. A long half-life (approximately 20 hours, based on limited data from premature infants (Barrett et al 1993).

Clonidine:

Clonidine acts centrally and decreases global sympathetic flow and is administered in adult experiencing withdrawal syndromes. Clonidine is less effective in adults in comparison with opioids in the management of withdrawal symptoms (Gowing et al., 2009).

Phenobarbital:

Phenobarbital is a barbiturate anticonvulsant. It is mostly administered as adjuvant therapy once the opiate dose is attained, it can be used as a key adjuvant with opioids or as a single primary therapy (Coyle et al., 2002). The phenobarbital half-life in neonates is 115 hours at 1 week and reduces to 67 hours after 4 weeks (Pitlick et al., 1978).

Treatment:

The best therapeutic remedy should seek to strike a balance between safety and effective care and also factor in the pharmacoeconomics aspect in the entire plan. .Apart from the treatment of NAS, many of these infants has pressing medical and social issues that require to be admitted in hospital. Physicians may consider weaning by volume to simplify dosage for parents and eradicate error. (Kuschel, C., 2007).

Pharmacologic intervention comparison for neonatal abstinence syndrome

Drug Attributes	Morphine[a]	Methadone[b]	Clonidine[c]	Buprenorphine[d]	Diluted Tincture of Opium[e]	Phenobarbital[f]
Class	Opiate	Synthetic opiate	Centrally acting adrenergic	Synthetic opiate	Opiate	Barbiturate
Action	Mu agonist	Mu agonist	Alpha 2 adrenergic agonist	Partial mu agonist	Mu agonist	Decrease hyperactivity in the CNS
Duration of action	Shorter half life 8 hours	Long-acting half life 26 hours	Long acting	Long acting	Variable	Long acting
Adverse effects	Respiratory depression	Prolonged Q-T interval	Rebound symptoms of increased BP and HR with abrupt cessation	Respiratory depression	CNS depression, respiratory distress, seizures, and hypotension	Oversedation Impaired sucking reflex
Special considerations	First-line therapy Frequent dosing	First-line therapy	Less sedative effects or respiratory depression	Able to titrate to high doses Needs more research on efficacy	Diluted oral morphine solution. No standard formulation: high morphine and opioid concentrations	Adjunctive therapy Outpatient monitoring and weaning Periodic blood level monitoring
Efficacy	More effective than phenobarbital	Trials inconclusive compared to morphine	↓ Finnegan scores with primary or adjunctive therapy	Decrease in duration of therapy when compared to morphine.	No difference between diluted tincture of opium and oral morphine	Improved outcomes as an adjunctive agent

CNS = central nervous system; DTO.

a Hudak & Tan (2012), Langenfeld et al. (2005), Ebner et al. (2007), Jackson et al. (2004).

b Bio et al. (2011), Jones et al. (2010).

c AAP (2012), Agthe et al. (2009), Leikin et al. (2009).

d Jones et al. (2010), Kraft et al. (2011).

e Langenfeld et al. (2005).

f Bio et al. (2011), Coyle, Ferguson, LaGasse, Liu, and Lester (2005), Isemann et al. (2011), Langenfeld et al. (2005).

CONCLUSION

The prevalence of NAS is increasing for infants exposed to opioids or recreational drugs in antepartum period. Since there is no specific remedy for infants, most systems rely on pharmacotherapy. Non-pharmacological and alternative therapies, although available have not gotten much attention in the literature. The huge consensus is to develop non-drug plan for entire predisposed children, to a need for pharmacological intervention, and evaluate their effectiveness frequently. Phenobarbital has been shown to be effective in the treatment of seizures associated with opioid withdrawal. It has been demonstrated that clonidine is effective and safe and is used as a second line drug treatment for NAS, which are resistant to opioid therapy. The concentration of methadone or buprenorphine present in breast milk is minute to treat NAS, so abrupt cessation of breast milk is not linked with exacerbation of NAS.

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