Journal of Pharmaceutical Research International

33(63A): 405-412, 2021; Article no.JPRI.80870
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Assessment of Drug Dependence in Neonates Due to Intra-Uterine Drug Exposure- Neonatal Abstinence Syndrome

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i63A35900

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80870

Review Article

Received 24 October 2021
Accepted 27 December 2021
Published 29 December 2021

ABSTRACT

A female, during her pregnancy, if consumes drugs exposes her fetus to the drug in its intra-uterine life. Once the drug enters the body, it sends information from VTA to the nucleus accumbens and then to the prefrontal cortex, activating the reward center in the brain. The fetus is exposed to this drug passing through the placenta. The drug binds to the mu receptors and causes hyperpolarisation of receptors. As a result, there is an increase in levels of dopamine. Due to this repetitive cycle, the fetal brain interprets these increased dopamine levels as resting dopamine levels. After delivery, the baby is now no longer under the drug influence. Due to abrupt cessation, the body cannot cope and undergoes withdrawal symptoms; this condition is known as *"Neonatal Abstinence Syndrome (NAS)."* The baby shows various symptoms like crankiness, irritation, loud crying, fever, jaundice, tremors, etc. The baby is treated with medicines that the same drug family is exposed to during intrauterine life, such as buprenorphine and methadone. The doses are given to help the infant adjust to the abrupt stoppage of the drug, gradually decreasing the dosage to help wean off the drug. Early and timely treatment with close observation of both the infant and the mother is crucial.

Keywords: Intra-uterine life; dopamine; withdrawal; NAS.

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1. INTRODUCTION

A female during her pregnancy has an intimate connection with her baby via the placenta. Almost everything that enters her bloodstream reaches her fetus via this placenta. Some substances can cross this placental barrier, while some cannot. Those that can cross are of concern if they risk hindering the fetus's development. There are several substances that cross this placental barrier and cause deformities that may be physical or can also hamper the mental development of the fetus. Such substances are called teratogenic. Congenital disabilities such as neural tube defects congenital heart defects are a few to name that may occur [1]. Many drugs are hence contraindicated in pregnancies due to this particular reason.

If a woman takes licit or illicit drugs during her pregnancy, she exposes her fetus to intra-uterine drugs [2]. As the drug crosses the maternal placenta, the fetus is now exposed to the drug consumed by its mother. Due to prolonged and continuous exposure to the higher levels of the drug, there is an increase in dopamine levels in both the mother and the foetus. The increased levels of dopamine are interpreted as usual by the fetal brain. Once the baby is born, there is a drop in dopamine levels due to no further drug exposure. This causes withdrawal symptoms. Due to not getting the previous levels of dopamine, the body demands to have those levels function as expected. The baby facing such withdrawal to the absence of further drug exposure suffers from a condition called "Neonatal Abstinence Syndrome."

The drug usage could be for medicinal purposes or recreational use by the mother. In both the cases, the mother's body develops dependency both physically and mentally. The most commonly drug used that causes NAS is opioids.

2. OBJECTIVE

We are assessing the most common drug used in NAS, identifying the reasons for prescribing such drugs.

One of the most difficult conditions while prescribing drugs to any female is during her pregnancy. A lot has to be kept in mind before giving any drug that will bring about physiological changes in the body during pregnancy. Many drugs are contraindicated in a few trimesters, while many are not advised to be taken throughout full term of pregnancy, i.e., all the three trimesters. Gases, nutrients, and waste products produced by foetal body are being taken away from fetus to mother and from the mother to the fetal body by a very close connection called placenta. So almost everything that circulates in the mother's blood system will also enter the foetal circulation. Many substances can thus either pass this placental barrier, while some cannot pass at all. The substances that cannot pass through this barrier are thus not considered as harmful for the foetal body. But those that can pass in minute quantities those that can pass completely possess a threat to the fetus. Placenta thus acts as a barrier but cannot prevent everything from passing to the foetus [3]. Almost every drug the mother consumes goes to her bloodstream and is passed on to her unborn baby [4].

They may cause various physiological changes and thus hinder growth and development of the foetus. Such hindrances cause deformities that can be either physical, mental, or both. Foetuses that undergo intra-uterine exposure to a few drugs have such disabilities once they are born. Such substances are considered to be teratogenic. This is the reason why many drugs are not allowed to be taken during pregnancy.

When in the womb, the foetus is exposed to a certain level of drug in its system. Hence the neonate's body starts undergoing withdrawal due to the abrupt cessation. On exposure to the drug by the fetus, the foetus' system initially considers this as foreign but soon adapts to these increased levels in its body. If the mother continues the drug used for a considerable amount of time, there is an increase in the levels of dopamine in both the mother and the fetus. Now once the baby takes birth, it is not under drug exposure, i.e., on being born, it is now no longer under the influence of the substance consumed by mother. This gives rise to withdrawal symptoms. Though not taken directly, the baby is now used to the levels of the increased drug in its system during its intra-uterine life. Due to such intra-uterine exposure, fetus develops a condition known as "Neonatal Abstinence Syndrome." The main reason for the dependence is the reward system in the brain. Due to the higher concentration of the drug in the body system, the brain now gets accustomed to a higher level of dopamine than what should have been that is considered as usual due to the action by reward system. Now the brain functions

as usual at these increased levels. If the mother continues usage of the drug, the fetal brain recognises these increased dopamine levels as usual. Now, once the baby is born, it is no longer exposed to the drug. The sudden stoppage of fetal exposure to the substance that the mother abused during her pregnancy causes drug withdrawal in the baby, a situation that is well known as Neonatal abstinence syndrome. (NAS) [2].

The most common drugs among opioids causing NAS are heroin and morphine. With improved and better drug manufacturing since past years, prescription opioids like hydrocodone, oxycodone, and opioid-containing combination products have shown neonatal withdrawal [1].

Prescription opioids are analgesics prescribed by physicians in cases of injury, surgery or dental work. Though taking such analgesics like morphine is contraindicated in pregnancy [1].

Heroin is an illegal street drug made from opioid morphine. It is found in white or brown powder or can be black, sticky tar heroin. It is either sniffed, smoked or injected. Many a times heroin is used by those who get addicted to prescribed drugs [5].

The other drugs abused are:

- Stimulants like cocaine, amphetamines [4]
- Antidepressant medicines such as selective serotonin reuptake inhibitors (SSRIs) [4]
- Alcohol, nicotine [4]
- Morphine [6]
- Tramodol [6]

The drug usage could be for medicinal purpose or recreational use. In both the cases, the mother's body develops dependency both physically and mentally. The most commonly drug used that causes NAS are opioids.

The symptoms include central and autonomic nervous system and gastrointestinal system.

The baby shows signs such as body shakes, tremors, seizures and convulsions, overactive reflexes (twitching), tight muscle tone. Fuzziness, excessive crying, high pitched cries, poor suckling or feeding, slow weight gain, irritability, breathing discomfort, uneasiness, fever, blotchy skin, sneezing, etc.

3. MORPHINE

Principal alkaloid in opium is morphine. Morphine is a pain medication that belongs to the opioid family of drugs. It exists naturally as a dark brown, resinous form. It is obtained from a plant, commonly called as poppy plant, *Papevar somniferous.*It changes the way a brain reacts to the sensation of pain.

Morphine releasing tablets and capsules are only used to relieve severe pain that cannot be controlled by the use of other painkillers. Morphine comes as a solution (liquid), an extended-release (long-acting) tablet, and as an extended-release (long-acting) capsule that can be consumes orally.

It interacts by binding to mu receptors (having highest affinity) in the central nervous system (CNS) as agonist. It has site specific depressant and stimulant action in the central nervous system. It is a strong pain killer. It works by showing actions through interneurons involved in gate channels in pain pathway impulses. Morphine produces calming effect. There is a loss of perception, a sense of detachment and concentration ability is diminished. Patients in pain and anxiety and addicts have known to have perceived a feeling as "pleasurable floating sensation [7]. If the female during pregnancy undergoes surgery and needs morphine as painkiller, and then the dosage is reduced suddenly, the body is not given time to readjust to the given smaller doses, she develops dependency.

4. MECHANISM OF ACTION OF OPIOID

When any opioid reaches the brain through bloodstream, the chemicals attach to the mu receptors which are specialised proteins [7]. They are present on opioid sensitive neurons [7]. The receptor-chemical interaction and linkage causes a feeling similar to reward/satisfaction/pleasure [7]. This feeling causes repeated use by abusers and thus habituation to its usage. On consumption of opioids the mesolimbic reward system in the brain (mid brain) is activated [7]. This drives the abuser to use the drug more frequently, eventually increasing dose and developing a tolerance.

Mesolimbic dopaminergic system is originated in the ventral tegmental area (VTA). It sends information from VTA to nucleus accumbens.

And from nucleus accumbens, information travels to prefrontal cortex, giving a sense of reward/satisfaction/pleasure. The neurons are under continuous suppression due to gamma-Aminobutyric acid (GABA) in the VTA. GABA supresses extra sensations of pleasure or reward. It occupies receptors and prevents the extra sensations all the time [8]. When a baby is exposed to morphine or morphine derivative or any kind of opioid, it causes hyperpolarisation of the receptors. This hyperpolarisation opens the way for dopamine to travel all the way to the receptors in nucleus accumbens. It occupies the post synaptic receptors and travels to prefrontal area giving the sense of reward and pleasure [8].

Hence there is an increase in the resting levels of dopamine concentrations in the brain. Thus, now the brain responds to these successive higher levels of dopamine on repeated use of the drugs. The person will now take more dosage of drug to offset the reduction to normal levels of dopamine. This repetitive feeling to have higher levels of dopamine giving a pleasurable feeling and satisfaction drives the person to use the drug at more frequent chances. This continuous dependency to achieve the rewarding feeling makes the person to abuse the drug and thus become an addict.

5. TOXICITY IN FOETUS

Due to having low molecular weight and having lowlipophilicity, they allow the opioid containing drugs to pass across placenta to the foetus easily. The drug accumulates in the foetal brain by surpassing the blood brain barrier [9].

The baby in womb is thus used to higher levels of dopamine in brain till mother continues drug usage and it keeps crossing placenta and reaches the foetus. The foetus being accustomed to higher levels of dopamine, suddenly cannot adjust to diminished levels that are considered to be normal for a non-exposed neonate after birth. Hence, the baby starts withdrawal symptoms as a result of cessation of drug passing in blood and subsequent lowered dopamine levels [10].

6. SIGNS AND SYMPTOMS

The symptoms may start immediately, 24-48 hours or even upto 5-10 days later [4].

The neonate might show signs of:

Loud and high-pitched crying, too much crying, irritated, seizures, vomiting, diarrhoea, fever, sleep problems, tight muscle tone [4], low birthweight, jaundice [6].

CNS symptoms include jitteriness, hyperirritability and tremors. This leads to disturbed sleep patterns and difficulty in maintaining calmness in the baby. Other possibilities include myoclonic jerks and seizures. Body functional instability leads to conditions like tachycardia, tachypnoea, and hyper or hypothermia. Skin perfusion alteration, leading to marks and spots on skin and sweating. Nasal congestion,frequent yawning, nasal flaring andexcessive sneezing may also be present [9,11].

Premature infants have been observed to have shown lesser severity and less severe symptoms [9,12,13].

7. REASONS FOR PAINS DURING PREGNANCY

Pain is a very common problem faced by a woman during her pregnancy. The problems can be related to obstetrics or may be non-obstetrics. The changes that occur physiologically and anatomically in the body are capable of producing pain in the body.

Due to the foetal weight in the womb, the mother often complaints of severe lower back pains. Because of the abdominal wall that stretches largely, there are chances of syndromes caused due to nerve entrapment. Sharp pains in lateral thigh and groin are seen [14].

Other pains maybe acute pancreatitis, gastric pains, iliac fossa pain due to kidney stones, urinary tract infections, headaches, migraines, etc.

8. DIAGNOSIS

Up until the withdrawal symptoms are not noticed, infants that are born to females who had secretly abused prescription opioids may not be identified as at risk [15].

The first and major primary diagnosis is by taking verbal past history of drug usage or drug abuse by the mother before and during pregnancy in a non-threatening, polite and without judgemental viewpoint. Report accuracy is very important with correct timeline history. This helps the physician know the last time the drug was used by the patient [4].

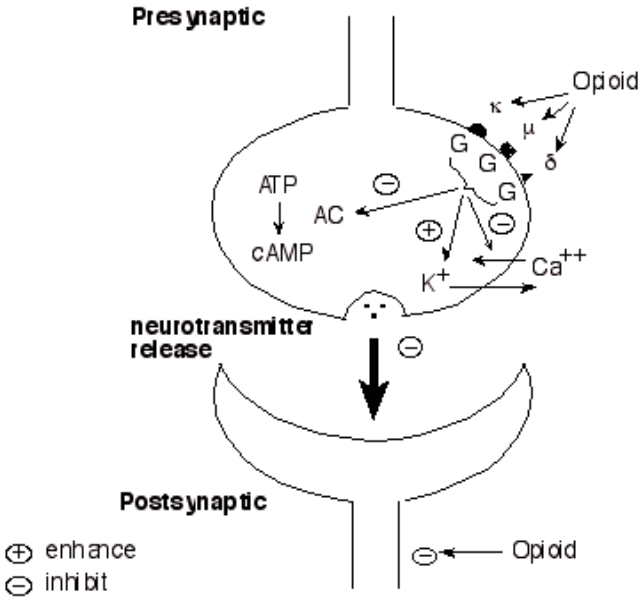

Fig. 1. Pre-post synaptic receptors

Not every time it is possible to get accurate history from the mothers with authenticity. So, it is necessary to examine the new born. To confirm in-utero drug exposure, there are various methods to check. Meconium (first stool passed by the infant), urine, cord blood, hair samples help in assessment. Urine testing may only confirm drug usage by mother a few days before delivery. Thus maternal drug usage may be confirmed within 2-4 days in the neonate's urine sample [9].

A delay in collection of urine sample from the infant may give false negative test report for drug exposure in prenatal life (in-utero). Hence it is very necessary to take the first sample of urine passed by the baby just after delivery. Meconium testing is a bit more accurate than the urine testing. Dating back to 20 weeks of gestation, it can identify the drug exposure. The metabolism difference in drug clearance of mother and foetus may also give false negative tests. Maximum number of opioids can be detected by either of these tests except synthetic or semisynthetic drugs. For authenticity and most accurate confirmation, maternal urine as well as foetal meconium sample must be collected for testing [9,16,17].

The "gold standard" for NAS assessment has been considered as the Finnegan Neonatal Abstinence Scoring System (FNASS) and its modified versions [18],[9]. It is used to check the severity of the neonatal abstinence syndrome. All infants that are highly suspected or are confirmed to have had the in-utero opioid exposure should have monitoring with a standard assessment instrument such as a Finnegan Scoring system [19]. A Finnegan score of >8 suggests opioid exposure, even in the absence of professed use during pregnancy.

9. TREATMENT

Buprenorphine is used as a new treatment for the treatment of maternal opioid addiction and appears to result in a milder withdrawal syndrome than methadone in cases of morphine [15]. Recent studies in the treatment of opioid-dependent pregnant women have suggested buprenorphine as an alternative treatment to methadone during pregnancy [20]. Methadone is a mu receptor agonist [21]. Rooming-in and breastfeeding may decrease the severity of withdrawal [15]. Prenatal counselling at home remedies are also an important part of treatment.

Methadone has been used in the past in the treatment of heroin. Buprenorphine is a partial opioid agonist. Naltrexone is an opioid agonist. It blocks opioid action. Non-addictive, and dependence is low [22].

Once the baby is born and withdrawal is under control, it is given small doses of medicines over time. It helps adjust the body being off the drug

after birth. The medicines used are usually of the same family of the drug that was used in-utero by the mother. The amount of medicine is slowly then decreased when the baby starts showing signs of improvement. This helps the baby wean off the drug. The medicines used are morphine, methadone and buprenorphine. Injecting fluids via i.v to the baby to prevent dehydration is necessary. A higher calorie diet is needed in the form of baby formula to compensate for the extra calories needed for growth as they have slower growth rate and difficulty in feeding. Due to the baby having jitteriness and crankiness, it is difficult for the baby to remain calm. It is very important to provide comfort and a suitable environment that is friendly for the baby. Rocking the baby in arms, covering it with warm blanket, giving the infant kangaroo care i.e. putting the baby on bare chest and giving skin-to-skin touch comfort, stay in with the baby in a dim and quiet room [6]. Breastfeeding is always encouraged (until and unless the mother is still on drugs or medication, using street drugs, under polydrug abuse or infected with HIV. It helps build a bond between the mother and the infant [2]. Breastmilk is considered the best for the baby's nutrition. It contains lots of vitamins, provides innate immunity and helps in growth and development. The babies that are breastfed have shown lesser severity of neonatal abstinence syndrome [23,4].

10. BUPRENORPHINE

On binding at mu opioid receptor, buprenorphine produces two different responses at different doses. At lower dose, it acts like methadone. But at higher dose, it behaves like naltrexone, blocking the receptors so strongly that it can precipitate withdrawal in highly dependent patients. Many clinical trials have shown that when it is used in a comprehensive treatment program with psychotherapy, buprenorphine has shown effectiveness similar to that of methadone. It has shown to not supress the consciousness and respiration as seen in case of overdose of methadone. This is the reason why buprenorphine is the newer treatment used than methadone [24-31].

11. CONCLUSION

Neonatal abstinence syndrome is a prevalent problem in developing and under developing countries. It is a burden on the health care system and physicians. Monitoring whether the child is responding to the given medication or there is requirement for an alternative treatment [4]. Opioids are a type of drugs with strong dependency. Neonates that were exposed to these drugs in intra-uterine life have shown drug dependence after birth. The most commonly used drugs that cause NAS are opioids. Be it prescribed drug or recreational, these drugs are harmful for the foetus and thus play a role in causing NAS.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/80870