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TREATMENT WITH OPIOIDS IN NEONATAL ABSTINENCE SYNDROME

Ariel Batista Santos Pascoal Silva
Student at: "Universidade de Vassouras", RJ, Brazil
http://lattes.cnpq.br/6306974449538338

Ana Claudia Zon Filippi
Advisor, anesthesiologist, professor at "Universidade de Vassouras", RJ, Brazil
http://lattes.cnpq.br/0654356407316622

Abstract: Neonatal Abstinence Syndrome (NAS) is a complex condition that affects neonates exposed to opioids during pregnancy. 1,196 articles were analyzed in databases, resulting in 22 articles selected following inclusion and exclusion criteria. The articles were selected from a 10-year period, from 2013 to 2023. The use of opioids by pregnant women is associated with a significant increase in the incidence of Neonatal Abstinence Syndrome, due to the passage of these substances through the placenta, leading to dependence fetal physics. Studies have demonstrated that buprenorphine pharmacotherapy in pregnant women with opioid use disorder is associated with better maternal and neonatal outcomes compared with untreated disorder. Buprenorphine, compared to methadone, has shown comparable maternal efficacy and less physiologic suppression of fetal heart rate, resulting in less severe neonatal abstinence syndrome. Methadone is widely prescribed for the treatment of opioid dependence during pregnancy due to its relative safety and effectiveness. The management of Neonatal Abstinence Syndrome involves non-pharmacological support measures, followed, in some cases, by pharmacological therapy. The relationship between maternal dose of buprenorphine or methadone and the incidence or severity of Neonatal Abstinence Syndrome is inconsistent in some studies. The lack of prospective studies on the nutritional management of infants with Neonatal Abstinence Syndrome has led to a variety of treatment approaches. In summary, Neonatal Abstinence Syndrome is a complex condition that requires a multidisciplinary approach for effective management. Understanding the factors that influence Neonatal Abstinence Syndrome and developing evidence-based treatment strategies are crucial to improving neonatal outcomes in infants exposed to opioids during pregnancy.

Keywords: *Neonatal abstinence syndrome; Opioids; Treatment*

INTRODUCTION

Neonatal Abstinence Syndrome (NAS) is a complex condition that affects neonates exposed to opioids during pregnancy. The use of opioids by pregnant women has been associated with a significant increase in the incidence of NAS (Neonatal Abstinence Syndrome), as these substances cross the placenta, leading to physical dependence in the fetus (DAVIS JM, et al. 2018).

Studies have demonstrated that buprenorphine pharmacotherapy in pregnant women with opioid use disorder is associated with superior maternal and neonatal outcomes compared to untreated opioid use disorder (JONES HE, et al. 2014). Additionally, buprenorphine has been compared to methadone during pregnancy, showing comparable maternal efficacy and less physiological suppression of fetal heart rate, resulting in less severe neonatal abstinence syndrome (JONES HE, et al. 2014).

The incidence of NAS (Neonatal Abstinence Syndrome) in the United States has increased significantly in recent decades, becoming a health problem (CZYNSKI AJ, LAPTOOK AR. 2013). Methadone has been widely prescribed for the treatment of opioid dependence during pregnancy due to its relative safety and effectiveness (JONES HE, et al. 2013). Studies have shown that methadone pharmacotherapy during pregnancy reduces the risk of fetal exposure to toxins associated with heroin use and improves outcomes (JONES HE, et al. 2013).

The management of NAS (Neonatal Abstinence Syndrome) generally involves non-pharmacological supportive measures, followed, in some cases, by pharmacological therapy to control persistent symptoms (ZIMMERMANN U, et al. 2020). However,

the relationship between maternal dose of buprenorphine or methadone and the incidence or severity of NAS has been inconsistent in some studies (JONES HE, et al. 2014). Studies have also investigated the relationship between maternal dose of methadone and other neonatal outcomes, such as birth weight and need for pharmacotherapy for NAS, with variable results (JONES HE, et al. 2013).

The lack of prospective studies on the nutritional management of infants with NAS (Neonatal Abstinence Syndrome) has led to a variety of treatment approaches, including the use of calorie-enhanced formulas or breast milk (BOGEN DL, et al. 2017). Studies have shown that babies exposed to methadone are more likely to lose excessive weight and return to their birth weight later than unexposed babies (BOGEN DL, et al. 2017).

NAS not only affects the neonatal period, but can also impact long-term developmental outcomes (CZYNSKI AJ, LAPTOOK AR. 2013). Babies with NAS are more likely to be readmitted to the hospital and experience growth and development problems (CZYNSKI AJ, LAPTOOK AR. 2013).

Given these questions, it is essential to understand the pharmacokinetics and clinical management of NAS in neonates exposed to opioids. Pharmacokinetic studies have focused primarily on intravenous administration of morphine in neonates, leaving a gap in knowledge regarding the enteral pharmacokinetics of morphine in neonates with NAS (Introduction 18). Therefore, it is necessary to investigate the pharmacokinetics of enteral morphine in neonates to improve treatment efficacy and reduce the duration of hospitalization (CZYNSKI AJ, LAPTOOK AR. 2013).

In summary, NAS is a complex condition that requires a multidisciplinary approach for effective management. Understanding the factors that influence the incidence and severity of NAS, as well as developing evidence-based treatment strategies, are crucial to improving neonatal outcomes in infants exposed to opioids during pregnancy.

Given the association of descriptors used, a total of 1,196 works were analyzed, 1,196 were selected from the PubMed database, 0 from the LILACS database and 0 from the SciELO database. Using the inclusion criteria: articles published over a period of 10 years (2013-2023), resulted in a total of 841 articles. Then, articles of the type clinical trial, randomized controlled clinical trial or newspaper articles were added as inclusion criteria, totaling 35 articles. Articles in Portuguese or English were selected, resulting in 35 articles. Then articles with free full texts were selected, resulting in 22 articles. After reading the abstracts, those that did not fit the topic covered or that were duplicates were excluded, totaling 18 articles, as illustrated in Figure 1.

Among the resulting articles, it can be observed that three main drugs were used to treat neonatal abstinence syndrome, morphine, Methadone and Buprenorphine. In all the studies analyzed, these drugs proved to be effective. In some of them, with treatment, patients' hospitalization time decreases. When analyzing all the studies together, it was not possible to identify which drug is the most effective among the treatments used, as the conclusions of each article present some differences between them. But it is undeniable that treatment with the drugs studied was effective in all of them, regardless of what caused the withdrawal, as described in Table 1.

DISCUSSION

Several pharmacological interventions have been proposed to treat NAS and minimize its adverse effects on infants. All studies were analyzed and compared on

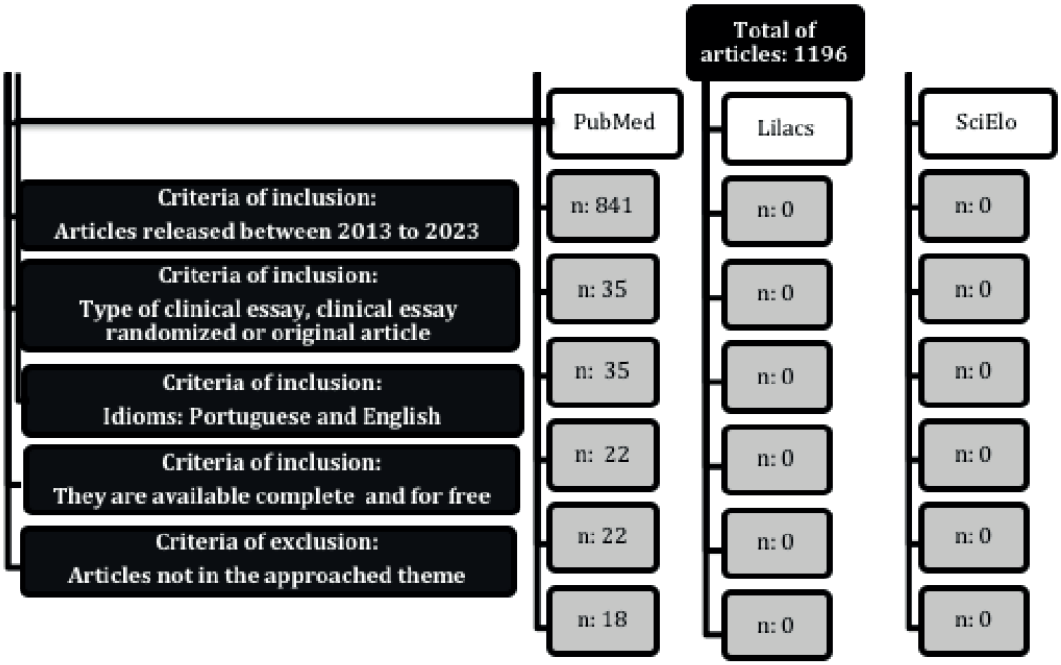

FIGURE 1: Flowchart for identifying articles in PubMed, LILACS and SciELO.

Author	Year	Sample	Treatment used	Result
Davis JM, et al.	2018	183	Methadone and morphine	Short-term outcomes were better in children who received methadone compared with morphine.
Kaltenbach K, et al.	2018	96	Methadone and Buprenorphine	**The results suggest that prenatal exposure to opioid agonists is not harmful to normal physical and mental development.**
Kraft WK, et al.	2017	63	Buprenorphine and morphine	Treatment with sublingual buprenorphine resulted in shorter treatment duration and shorter hospital stays than treatment with oral morphine.
Sutter MB, Watson H, et al.	2022	61	Methadone and morphine	Methadone-treated infants received up to 3 times more opioid-based morphine equivalents than morphine-treated infants and had more transfers to the NICU for oversedation.
Moore JN, et al	2018	28	Buprenorphine	The person has demonstrated beneficial effects of buprenorphine in the treatment of neonatal abstinence syndrome.
Czynski A, Laptook A, et al	2023	Em andamento	Morphine and methadone	Ongoing
Flannery T, Davis JM, et al.	2020	116	Morphine and methadone	It was effective, although presumptive measures of NAS severity can be aggregated to develop an index that predicts developmental outcomes at 18 months.
Kreitinger C, Gutierrez H, et al.	2016	70	Methadone and alcohol	Pre-exposure to alcohol was not associated with the severity of neonatal abstinence syndrome.

Wiles JR, et al.	2015	40	Methadone	It was effective and demonstrated that it can reduce the dosage used and shorten hospitalization time.
Czynski AJ, et al	2020	61	Morphine and methadone	Infants treated with morphine or methadone had similar short- and long-term neurobehavioral outcomes.
Nayeri F, et al.	2015	60	Morphine and Phenobarbital	There was no difference in length of stay between those treated with morphine and those treated with phenobarbital.
Peltz G, et al.	2023	22	Ondansetron and opioids	Treatment with ondansetron reduced the severity of symptoms and there was indication that it could reduce length of stay.
Jones HE, et al.	2014	12	Methadone, buprenorphine and tobacco	Regardless of prenatal exposure to methadone or buprenorphine, heavy smoking was associated with poorer birth outcomes.
Zimmermann U, et al.	2020	2013	Morphine, chlorpromazine and phenobarbital	Morphine alone was able to control symptoms in almost all babies; it may be preferred over the other two medications.
Jones HE, et al.	2013	73	Methadone	Methadone maintenance treatment of opioid-dependent pregnant women has been found to be associated with improved maternal and neonatal outcomes.
Czynski AJ, Laptook AR.	2013	502	Morphine and methadone	It has positive effects on treatment, used alone or together.
Bogen DL, et al.	2018	49	Methadone	Early initiation of high-calorie formulas for infants with prenatal methadone exposure may be beneficial for weight gain.
Liu T, Lewis T, et al	2016	52	Morphine	It was effective for the treatment of neonatal abstinence syndrome

TABLE 1: Main conclusions obtained from articles related to opioid treatment in neonatal abstinence syndrome.

Source: Authors (2024)

different therapeutic approaches, in addition to discussing the pharmacokinetics of drugs commonly used in the treatment of NAS, such as morphine, buprenorphine and methadone. (LIU T, et al. 2016).

Gradual weaning from opioids is a common strategy in the treatment of NAS, aiming to reduce withdrawal symptoms without causing adverse effects. The effectiveness of rapid weaning (15% stabilization dose reduction) versus slow weaning (10% stabilization dose reduction) was addressed, showing that both approaches can be effective, but without consensus on the ideal rate of reduction. of the dose. (DAVIS JM, et al. 2018).

The choice of food formula also plays an important role in the management of NAS. The use of high-calorie formulas in babies exposed to methadone has been investigated, showing promising results regarding earlier return to birth weight and greater daily weight gains. However, variation in the nutritional management of NAS between hospitals highlights the need for clear guidelines in this regard. (BOGEN DL, et al. 2017).

The pharmacokinetics of morphine in neonates with Neonatal Abstinence Syndrome (NAS) is a crucial aspect to be considered in its treatment. We can observe that morphine is rapidly absorbed after oral administration, but its oral bioavailability in neonates (46.3%) is higher than that in healthy adults (23.9%). This suggests greater absorption and lower systemic clearance of morphine in neonates, which may influence the dose and frequency of administration required to achieve and maintain an adequate therapeutic effect. Furthermore, the pharmacokinetics of morphine in neonates may be affected by differences in the expression of hepatic metabolic enzymes, such as UGT2B7, and by liver size in relation to body weight, which may result in greater bioavailability and reduced systemic clearance of morphine. damn it. This information is essential to ensure the efficacy and safety of using morphine in the treatment of NAS in neonates. (LIU T, et al. 2016).

In addition to morphine, buprenorphine and methadone are common treatment options for NAS. Buprenorphine is a partial agonist of the mu and kappa opioid receptors, with less potential to cause dependence and adverse respiratory effects than methadone. The observations address the use of buprenorphine in the treatment of NAS, highlighting its efficacy and safety compared to methadone (KRAFT WK, et al. 2017), (KREITINGER C, et al. 2015).

On the other hand, methadone is a full agonist of mu opioid receptors, most widely used in the treatment of NAS due to its long half-life and pharmacokinetic stability. When comparing the use of methadone versus morphine in the treatment of NAS, it was shown that methadone can result in a shorter treatment duration and less need for adjuvant therapy. (CZYNSKI AJ, et al. 2019).

The pharmacokinetics of buprenorphine and methadone in neonates with NAS are not yet completely elucidated, but studies suggest that buprenorphine is rapidly absorbed after sublingual administration and has a longer half-life than morphine. Methadone, on the other hand, is well absorbed orally and has a prolonged half-life, which allows for less frequent dosing and stability in controlling withdrawal symptoms. (KRAFT WK, et al. 2017), (KREITINGER C, et al. 2015) (CZYNSKI AJ, et al. 2019).

Gradual weaning from opioids is a common strategy to reduce withdrawal symptoms in neonates with NAS. Both rapid weaning and slow weaning have been effective, but there is still no consensus on the best approach. This highlights the need for further research to determine the optimal rate of opioid dose reduction in neonates with NAS. (DAVIS JM, et al. 2018).

The choice of food formula is also crucial in the treatment of NAS. The use of high-calorie formulas has shown promising results regarding earlier return to birth weight and greater daily weight gains. However, it is important to consider the variation in nutritional management of NAS between hospitals and the need for clear guidelines in this regard. (BOGEN DL, et al. 2017).

The study of morphine pharmacokinetics in neonates with NAS was essential for the integration of previous knowledge of morphine pharmacokinetics. These data are important to optimize the dose and frequency of administration of morphine in the treatment of NAS. (LIU T, et al. 2016).

In addition to morphine, buprenorphine and methadone are common treatment options for NAS. Buprenorphine has been effective and safe in the treatment of NAS, with less potential to cause dependence and adverse respiratory effects than methadone.

This highlights the importance of considering buprenorphine as a viable alternative to methadone in the treatment of NAS. (KRAFT WK, et al. 2017) (KREITINGER C, et al. 2015).

On the other hand, methadone is widely used in the treatment of NAS due to its long half-life and pharmacokinetic stability. Compared to morphine, methadone may result in shorter treatment duration and less need for adjuvant therapy, making it a valuable option in the management of NAS. (CZYNSKI AJ, et al. 2019).

The pharmacokinetics of buprenorphine and methadone in neonates with NAS are not yet completely elucidated, but studies suggest that both drugs are well absorbed and have a prolonged half-life. This allows for less frequent dosing and stability in controlling withdrawal symptoms, making them effective options for treating NAS. (KRAFT WK, et al. 2017) (KREITINGER C, et al. 2015) (CZYNSKI AJ, et al. 2019).

In conclusion, pharmacological interventions in NAS are diverse and increasingly aimed at optimizing treatment and minimizing adverse effects on infants. Understanding the pharmacokinetics of the drugs used is essential to ensure the efficacy and safety of these treatments. Future research must focus on evaluating the comparative effectiveness of these approaches and identifying strategies to improve long-term outcomes for infants with NAS.

CONCLUSION

The use of opioids by pregnant women has been associated with a significant increase in the incidence of NAS, as these substances cross the placenta, leading to physical dependence in the fetus. Studies have demonstrated that buprenorphine pharmacotherapy in pregnant women with opioid use disorder is associated with superior maternal and neonatal outcomes compared with untreated opioid use disorder. Additionally, buprenorphine has been compared to methadone during pregnancy, showing comparable maternal efficacy and less physiologic suppression of fetal heart rate, resulting in less severe neonatal abstinence syndrome.

The incidence of NAS in the United States has increased significantly in recent decades, making it a public health problem. Methadone has been widely prescribed for the treatment of opioid dependence during pregnancy due to its relative safety and effectiveness. Studies have shown that methadone pharmacotherapy during pregnancy reduces the risk of fetal exposure to toxins associated with heroin use and improves obstetric outcomes. Management of NAS generally involves non-pharmacological supportive measures, followed in some cases by pharmacological therapy to control persistent symptoms. However, the relationship between maternal

dose of buprenorphine or methadone and the incidence or severity of NAS has been inconsistent in some studies. Studies have also investigated the relationship between maternal dose of methadone and other neonatal outcomes, such as birth weight and need for pharmacotherapy for NAS, with variable results. The lack of prospective studies on the nutritional management of infants with NAS has led to a variety of treatment approaches, including the use of calorie-enhanced formulas or breast milk. Studies have shown that babies exposed to methadone are more likely to lose excessive weight and return to their birth weight later than unexposed babies. NAS not only affects the neonatal period, but can also impact long-term developmental outcomes. Babies with NAS are more likely to be readmitted to the hospital and have problems with growth and development. Given these questions, it is essential to understand the pharmacokinetics and clinical management of NAS in neonates exposed to opioids. Pharmacokinetic studies have focused primarily on intravenous administration of morphine in neonates, leaving a gap in knowledge regarding the enteral pharmacokinetics of morphine in neonates with NAS. Therefore, it is necessary to investigate the pharmacokinetics of enteral morphine in neonates to improve treatment efficacy and reduce the duration of hospitalization. In summary, NAS is a complex condition that requires a multidisciplinary approach for effective management. Understanding the factors that influence the incidence and severity of NAS, as well as developing evidence-based treatment strategies, are crucial to improving neonatal outcomes in infants exposed to opioids during pregnancy.

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