www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2013;2(2):e020231
doi: 10.7363/020231

Editorial

Neonatal abstinence syndrome: a never ending story!

Johannes N. van den Anker

Division of Pediatric Clinical Pharmacology, Children's National Medical Center, Departments of Pediatrics, Integrative Systems Biology, Pharmacology & Physiology, George Washington University School of Medicine and Health Sciences, Washington, District of Columbia, USA

Proceedings

Proceedings of the 9th International Workshop on Neonatology · Cagliari (Italy) · October 23rd-26th, 2013 · *Learned lessons, changing practice and cutting-edge research*

Keywords

Abstinence syndrome, pregnancy.

Corresponding author

Johannes N. van den Anker, Children's National Medical Center, Department of Pediatrics, 111 Michigan Avenue, NW, Washington, DC 20010; phone: +1 202 476 2893; fax: +1 202 476 3425; email: jvandena@cnmc.org.

How to cite

van den Anker JN. Neonatal abstinence syndrome: a never ending story! J Pediatr Neonat Individual Med. 2013;2(2):e020231. doi: 10.7363/020231.

Introduction

In recent years there has been a shift from abuse of classical opioids such as heroin, morphine and methadone to abuse of prescription opioids such as hydrocodone, hydromorphone and oxycodone. This shift is in line with the significant increase in the prescription of opioids in the U.S. during the last ten years [1]. In 2011, there were 238 million prescriptions for opioids filled by U.S. pharmacies compared to 174 million in 2000. This surge in prescription rates has been associated with even more important increases in opioid abuse and associated fatalities. One of the most interesting findings

was related to the dramatic rise in hydromorphone use for several pain-related conditions that are often evaluated in emergency departments across the nation. Hydromorphone is a very potent mu-opioid receptor agonist with significant euphoric effects and relatively few adverse effects, which increases its potential for abuse.

This might have profound implications as short-term pain control may be achieved in the emergency department, but increased opioid use could contribute to later dependence. The concern over future dependence comes from the "likeability" of the experience where a very pleasant feeling is coupled with the analgesic effect. This may be potentiated by favorable pharmacologic properties, such as onset of action, and fewer adverse effects, such as flushing or vomiting. Studies suggest oxycodone has the greatest "likeability" and abuse potential, followed by hydrocodone and hydromorphone. This shift from classical opioids to prescription opioids is also reflected in the increased frequency of use of these medications during pregnancy and as an ultimate consequence we encounter more and more newborn infants with neonatal abstinence syndrome (NAS) caused by oxycodone, hydrocodone and hydromorphone [2].

Neonatal abstinence syndrome (NAS)

NAS is the result of fetal exposure to illicit or prescription drugs taken by the mother prenatally. Neonatal withdrawal symptoms have been noted following antenatal exposure to a number of drugs such as opioids, benzodiazepines, and selective serotonin reuptake inhibitors. A recent survey in the United States of America showed that around 16% of teenagers and 7% of women between the ages of 18 and 25 use illicit drugs during their pregnancies. NAS is a complex of symptoms, caused by acute withdrawal of the illicit drug(s) used by their mothers during pregnancy, seen in neonates hours or days after being born. NAS is primarily linked with use of morphine-like substances during pregnancy. However, other drugs have also been linked with this syndrome. Characteristic signs of NAS are diverse and consist of increased irritability, hypertonia, tremors, feeding intolerance, vomiting, watery stools, fever, tachypnea, and seizures. Symptoms of this syndrome have been seen in 60-80% of neonates who were exposed to morphine-like substances such as heroin or methadone during their stay in utero. In addition to the more familiar reason of developing NAS as outlined above, many newborn infants develop NAS during their stay in the neonatal intensive care unit (NICU) due to prolonged exposure to opioids prescribed to them to manage pain and stress [3].

Treatment of opioid dependence during pregnancy: challenges and opportunities

Decreased fetal growth, increased fetal mortality, and an increased risk of HIV infection are just a few of the major public health issues caused by prenatal exposure to opioids [4]. In an attempt to improve the fetal and neonatal outcome of opioid addicted pregnant women methadone or buprenorphine are prescribed [5]. At this moment methadone, a full mu-opioid agonist, is still the first choice treatment for opioid dependence during pregnancy. However, as an alternative buprenorphine, a partial mu-opioid agonist, is increasingly being used in this situation. Both drugs cross the placenta but there is currently still very little knowledge available concerning the clinical pharmacology of methadone and buprenorphine in the opioid addicted pregnant woman. Issues such as how much of both drugs reach the fetus, what is the relation between fetal serum concentrations and the development of neonatal abstinence syndrome (NAS), what is the relation between concentrations of these drugs in the mother and in the fetus or the neonate immediately after delivery are just a few examples of questions that need to be investigated to further improve the treatment and outcome of both the mother and her infant. There is sufficient data to support that methadone-assisted treatment during pregnancy results in better outcomes for pregnant women, fetuses and newborns as compared to use of heroin or other illicit opioids. Moreover, very recent data not only confirms the effectiveness of the use of methadone in opioid addicted pregnant women but nicely shows that the use of buprenorphine is associated with clinically relevant less severe NAS in the offspring of these women as compared to the women who were treated with methadone [6]. The infants of the mothers who were prenatally exposed to buprenorphine needed not only a reduced amount of morphine to treat the symptoms of their withdrawal but also during a shorter time frame and as a consequence they could be discharged sooner as compared to the infants of mothers treated with methadone. The reasons behind this clinically and economically important difference between using methadone versus buprenorphine in pregnant opioid addicted women still need to be elucidated.

Genetic differences in drug handling might be of importance but as outlined earlier many questions persist concerning the clinical pharmacology of these frequently used medications in this patient population. Scientific answers to these questions might help us in finding a more tailored approach to the pharmacological management of these women and their fetuses.

Why has there not been a complete switch from the use of methadone to buprenorphine in the opioid-addicted pregnant population? The reason behind this reluctance of solely prescribing buprenorphine has to do with the fact that in the pivotal study comparing methadone and buprenorphine the women who were prescribed buprenorphine were more likely to drop out of the study. There was clearly less satisfaction in the pregnant women exposed to buprenorphine as exposed to methadone and this may be caused by the fact that buprenorphine is a partial mu-opioid agonist and increasing the dose clearly will not result in more effect. For health care providers and caregivers this finding is potentially worrisome because of the fact that if the pregnant woman needs more opioids and increasing the dose buprenorphine will not give her more relief, these women will start searching for other means to fulfill their opioid needs. Clearly this will result in decreased compliance with buprenorphine and will put these women and their fetuses at an increased risk of being in a less controlled situation. As a consequence, the fact that methadone was more liked in this comparative investigation underscores the importance of continuing to prescribe methadone in women who are having opioid dependency and who are not reaching a stable and satisfactory situation with the use of buprenorphine.

At this moment it is very clear that there is an urgent need to understand better the clinical pharmacology of both methadone and buprenorphine that will incorporate pharmacokinetics, pharmacodynamics and pharmacogenetics in order to study factors that will allow us to decipher different subsets of pregnant women [7]. Some of these subsets might be perfectly treatable with buprenorphine whereas other subsets will need methadone to reach a satisfactory situation for both pregnant woman and their fetus. Until that moment health care providers have to tailor their treatment based on their experience in treating opioid-addicted pregnant women with the ultimate goal to reach optimal adherence to the treatment to assure the best outcomes for mother and child.

Treatment of neonatal abstinence syndrome: challenges and opportunities

In general there are two ways for a neonate to develop opioid withdrawal symptoms. The first one is related to exposure to opioids in utero and as outlined earlier these opioids may be illicit drugs such as heroin, prescription opioids such as oxycodone, hydrocodone and hydromorphone, or opioids used to treat opioid addiction during pregnancy such as methadone and buprenorphine. The second is related to prolonged exposure to opioids such as fentanyl or morphine to treat painful and/or stressful situations during their stay in the neonatal intensive care unit (NICU). Irrespective of the ways the neonate develops NAS there are two pharmacological treatment strategies that are routinely used for NAS. One of these is opioid substitution with methadone or buprenorphine and the other one is opioid replacement with morphine, methadone or buprenorphine combined, if needed, with drugs such as phenobarbital, clonidine or more recently dexmedetomidine [8].

The major challenges we are currently faced with in the area of treatment of NAS are the lack of a validated abstinence scoring system for neonates who develop NAS after being treated with opioids during their stay in the NICU, lack of effectiveness of the use of phenobarbital despite its use for several decades, questions about how to use alpha-2-adrenergist agonists such as clonidine and dexmedetomidine, and which of these agonists to use in what kind of circumstance. These are just a few of the challenges we are confronted with. Surely, in addition, there are questions about the use of buprenorphine versus methadone in NAS that are clearly echoing the same questions that are asked and investigated in opioid addicted pregnant women.

In NAS, the use of buprenorphine has been explored in two open label, placebo controlled trials indicating that the use of buprenorphine results in less morphine use to treat NAS and also less duration of treatment resulting in earlier discharge home. This might indicate that buprenorphine might become the first line of treatment for these neonates in the near future. However, we need to assure that long term follow-up will be performed in an attempt to see if these short term advantages do not come with long term unwanted health issues.

The use of phenobarbital for decades has not resulted in a definite answer about its effectiveness in NAS. There are specific clinical pharmacology

issues concerning phenobarbital that warrant attention. A rapid change in its disposition (i.e., rapidly changing clearance of phenobarbital due to developmental changes) is one of these, whereas the induction by phenobarbital of several liver and intestinal enzyme systems will result in significant increases in the clearance of other drugs.

Finally, the emergent use of alpha-2-adrenergic agonists such as clonidine and dexmedetomidine as part of combination therapy for mitigating the symptoms of opioid withdrawal has resulted in the design and conduct of several studies to find the right use, right dose and right duration of treatment of these medications. At this moment there is more clinical experience with clonidine for use in NAS but several studies with dexmedetomidine are currently designed to see if a more pure alpha-2-agonist might be an even better choice.

To summarize it has become clear that there is a shift from the use of heroin, morphine and methadone to the use of prescription opioids hydrocodone, hydromorphone and oxycodone and in many parts of the USA this has become a real epidemic. A very recent perspective in the New England Journal of Medicine (Sept 12, 2013) links this to "abusive prescribing of controlled substances" [9]. As a consequence opioid addiction during pregnancy not only has increased but it also has shifted to these prescription opioids. Treatment of opioid addiction in pregnant women has as goal to move away from illicit or prescription opioid use during pregnancy to the use of much longer acting drugs such as methadone or buprenorphine to assure a more controlled situation resulting in a significant better outcome for mother and child. For the neonate treatment primarily consists of replacing opioids to treat NAS followed by a treatment plan tailored to the individual newborn to assure the best possible short and long term developmental outcome for these vulnerable infants.

Declaration of interest

The Author declares that there is no conflict of interest.

References

1. Maxwell JC. The prescription drug epidemic in the United States: a perfect storm. Drug Alcohol Rev. 2011;30(3):264-70.
2. Hayes MJ, Brown MS. Epidemic of prescription opiate abuse and neonatal abstinence. JAMA. 2012;307(18):1974-5.
3. Patrick SW, Schumacher RE, Benneyworth BD, Krans ED, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA. 2012;307(18):1934-40.
4. Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. Am J Obstet Gynecol. 2011;204(3):259,e1-4.
5. Jones HE, Finnegan L, Kaltenbach K. Methadone and buprenorphine for the management of opioid dependence in pregnancy. Drugs. 2012;72(6):747-7.
6. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320-31.
7. Yuferov V, Levran O, Proudnikov D, Nielsen DA, Kreek MJ. Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment. Ann N Y Acad Sci. 2010;1187:184-207.
8. Bio LL, Siu A, Poon CY. Update on the pharmacologic management of neonatal abstinence syndrome. J Perinatol. 2011;31:692-701.
9. Betses M, Brennan T. Abusive prescribing of controlled substances – a pharmacy view. New Engl J Med. 2013;369(11):989-91.