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Introduction

Infants exposed in utero to opioids will demonstrate a withdrawal syndrome known as the neonatal abstinence syndrome (NAS). Buprenorphine is a long acting opioid with therapeutic use in medication-assisted treatment of opioid dependency in adults and adolescents. Emerging data from clinical trials and treatment cohorts demonstrate the efficacy and safety of sublingual buprenorphine for those infants with NAS who require pharmacologic treatment. Pharmacometric modeling will assist in defining the exposure-response relationships and facilitate dose optimization.

Neonatal Abstinence Syndrome

The placental transfer of drugs from mother to the fetus is well described. The developmental kinetics of drug permeability at the fetal "blood brain barrier" in humans is not fully defined, but is clearly immature early in pregnancy.[1] Many prescribed medications or drugs of abuse can impact postnatal outcomes, particularly with chronic use during pregnancy. Some substances cause neonatal symptomatology which is a direct effect of maternal transfer of the xenobiotic to the neonate. This is characteristic of a toxidrome. For example, intrauterine cocaine exposure is associated with tremors, high pitched cry and autonomic instability in the infant that is self-limited and improves as the drug is cleared from the system.[2] Other psychoactive agents are associated with symptoms that emerge as drug concentration falls within the neonate, indicating a withdrawal syndrome. Opioids, serotonin reuptake inhibitors,[3] nicotine,[4] and antipsychotics[5] all can cause withdrawal or adaptation symptoms. The term neonatal abstinence syndrome is non-specific. While the bulk of morbidity and symptoms are due to withdrawal to opioids, concomitant maternal use of other drugs associated with withdrawal symptoms is common. These exposures typically will worsen NAS symptoms and duration,

but exposures are difficult to quantify in practice and ultimately do not impact management decisions. Others, including the FDA, advocate use of the term neonatal opioid withdrawal syndrome (NOWS) to more specifically link symptoms to opioid exposure.[6] For the purposes of this review, the more commonly and general term NAS will be used to implicitly describe withdrawal symptoms driven primarily by in utero opioid exposure.

Physician prescription of opioids occurs between 14-37% of pregnancies,[7] but the majority are for a short duration and not associated with neonatal withdrawal. Prolonged in utero exposure to opioids is requisite for a withdrawal syndrome, though a threshold exposure has not been established and dose of maternal methadone is only weakly associated with neonatal symptoms.[8] Cardinal manifestations of neonatal opioid withdrawal are grouped into CNS, autonomic and gastrointestinal domains. Seizures are of greatest concern, but are uncommon in the current era of earlier recognition and treatment. NAS symptoms have clinical impact mainly on feeding, with attendant negative effects on growth and development. Non-pharmacologic treatments should be used in all infants with in utero exposure to opioids. There is not a universal definition of what constitutes a non-pharmacologic treatment, but common measures include the infant rooming in with the mother,[9] encouraging breast feeding,[10] multiple small feedings, swaddling,[11] and minimization of stimuli. Conceptually all infants should be considered to be along a spectrum of symptom severity. Even with use of non-pharmacological interventions, over half of infants with signs of withdrawal will require pharmacologic treatment.

Current Pharmacologic approaches to NAS

The need for pharmacologic treatment, and titration of dose is guided by a symptom score. The Finnegan scoring instrument[12] is the most widely used, but local variations are common. The MOTHER NAS score,[13] a modification of the Finnegan instrument, is standardized and is the most commonly

reported in clinical trials. An opioid is the primary therapy,[14] using a strategy of titrating doses to control symptoms and slowly weaning down. Morphine is used at 80% of centers in the US, with methadone being used in the remainder.[15] Phenobarbital or clonidine are used as adjunctive therapies in conjunction with an opioid when either maximum opioid dose has been reached, or in an initial co-administration with the goal of reducing opioid exposure. There is significant site to site heterogeneity in pharmacologic regimens, including starting and maximum dose, uptitration and weaning parameters.[16] There is a lack of definitive trials to guide therapy, though results of a multicenter trial comparing methadone and morphine (NCT01958476), will provide some guidance between these two drugs. There is a similar lack of consensus of the role of adjunctive therapy. Differing regimens employ the addition of clonidine or phenobarbital at maximum dose of opioid, or the use of either agent in parallel with the opioid, or as an opioid free monotherapy. Phenobarbital is a more non-specific CNS depressant and is believed to be particularly useful in polysubstance exposures, though there are theoretical concerns about neurotoxicity.[17] Clonidine has a mechanism more specific to opioid withdrawal and has better evidence base of randomized trials, but it is used at less than 10% of hospitals treating NAS. [15]

Implications of adult medically assisted therapy to neonatal therapies

Methadone and buprenorphine are the two primary treatments for opioid use disorder. Short acting opioids such as morphine are not used in adults as maintenance replacement. The opioid use disorder is defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is a series of maladaptive behaviors prompted by physical tolerance and withdrawal symptoms. These behaviors are associated with significant morbidity and mortality over age matched cohorts, primarily due to accidents, overdose, infection and violence. Treatment with methadone or buprenorphine compared to no long acting opioid reduces all-cause mortality by approximately 30%.[18] Substitution therapy has been examined primarily with illicit opioids, but appears effective in prescription opioid dependency as

well.[19] Cochrane reviews suggest that in aggregate, methadone has an efficacy advantage over buprenorphine in retaining patients in maintenance opioid replacement therapy.[20] However, at medium or high dose ranges, efficacy is similar. Infants with NAS have physical dependency, but none of the maladaptive behaviors associated with addiction. As such, extrapolation from adult therapeutics is somewhat limited. Relief from withdrawal symptoms is a pharmacodynamic endpoint better suited to extrapolation from adults to neonates than retention in a drug treatment program or urine drug screen results. For the acute control of withdrawal symptoms in adults, buprenorphine has improved efficacy relative to clonidine, and possibly to methadone.[21] Anecdotal clinician observations suggest buprenorphine may have an easier transition to the final weaning doses than methadone.

Buprenorphine in Pregnancy

There is high quality evidence demonstrating improved neonatal outcomes when mothers are maintained on opioid replacement therapy throughout pregnancy. Optimal therapeutic approaches are not solely pharmacologic, but combine pharmacologic opioid replacement with intensive counseling. Attempting to wean a pregnant woman off of opioid replacement has a high risk of relapse, and is commonly associated with patient substitution of illicit for prescribed of opioid replacement. This is considered only in cases with compelling indication under intense supervision.[22] Methadone has been the standard replacement opioid during pregnancy, with a recent increase in buprenorphine as the primary opioid. buprenorphine has been associated with lower risk of preterm birth and improved in utero growth parameters compared to methadone maintenance, without evidence of increased harms based on 3 randomized controlled trials and 15 cohort trials.[23] While in the landmark MOTHER trial maternal buprenorphine did not significantly reduce the number of infants who required pharmacologic treatment for NAS, it did reduce the duration of therapy and total morphine dose compared to methadone.[13] The dose of buprenorphine transferred during breastfeeding is low,[24] and the practice

is encouraged in most stable mothers not actively abusing medications.[25,26] There is no evidence that the maternal treatment with buprenorphine or methadone should drive the subsequent choice of pharmacologic treatment of NAS. The time to emergence of NAS symptoms following buprenorphine is similar to methadone exposure at 36-60 hours in most infants, though there are occasional cases of more prolonged time course. Anxiety and depression incidence are higher in women with opioid use disorders,[27] so concomitant benzodiazepine[28] or anti-depressant exposure[29] are common and can prolong the emergence time of symptoms.

Buprenorphine PK

Buprenorphine has agonism at delta, and opioid receptor-like (ORL1) receptors and antagonism at the kappa receptor. However it is agonism at the mu opioid receptor is thought to be the primary mode of action in reducing withdrawal symptoms and decreasing the effect of other exogenous opioids. Oral administration is not feasible due to a large first pass metabolism. The high degree of lipophilicity allows effective sublingual dosing. Ethanolic solutions are absorbed from the sublingual mucosa in adults with an absolute bioavailablity of 28-51%.[30,31] This occurs in 2-4 minutes, and longer retention times are not associated with increased systemic exposure.[30,32] Early publications and the product label of IV buprenorphine list a short elimination half-life. This is artefactual due to lower sensitivity and non-specificity of earlier radioimmune assays, along with low therapeutic serum concentration due to potency of buprenorphine.[33] Mean terminal elimination in adults after IV dosing of doses of 2 through 16 mg with a sensitive assay is 25 +/- 1 hour with a volume of distribution of ~800 L.[34] Administration by the sublingual compared to IV administration increases volume of distribution with the oral mucosa acting as a reservoir, which accounts for a prolonged elimination half-life up to 24-42 hours. The typical sublingual tablet dose range used in adults is between 4-24 mg/day, with the majority of patients controlled with 16 mg or less. Two mg of buprenorphine causes occupancy of 40% of mu opioid

receptors, while at 16 or 32 mg >80% of receptors were occupied.[35,36] Peak serum concentration is 0.5-1, 5-6, and 13-14 ng/ml for 2, 16 and 32 mg sublingual tablets, respectively.[16] Buprenorphine pharmacokinetics predict receptor occupancy reasonably well, and by linking to pharmacodynamic response, ~50-60% mu opioid receptor occupancy provides relief of withdrawal symptoms.[37] This degree of occupancy correlates with a serum concentration of 1.0 ng/ml, consistent with an estimate of 0.7 ng/ml from other investigation in opioid experienced subjects.[38] The concentration needed to suppress reinforcing and subjective effects of abused opioids, which is less relevant in NAS, is estimated to > 3 ng/ml.[37] While these data are useful, caution should be used in extrapolation to the neonatal population. Opioid exposure may upregulate mu opioid receptor density compared to healthy volunteers.[35] Differences in body water and fat composition between neonates and adults may impact the distributive characteristics. Lastly, while there are parallels in the pathophysiology of withdrawal from opioids between adults and neonates, the biology in newborns is not as well characterized and more complicated due to the neurodevelopmental trajectory in newborns.

Buprenorphine Clinical Studies in NAS

An open label, active control, phase 1 investigation was the first use of sublingual buprenorphine in NAS.[39] In the first cohort 26 term infants without exposure to benzodiazepines, buprenorphine demonstrated a significant reduction in length of treatment and stay compared to standard of care oral morphine. (Table 1) The treatment protocol for both arms used escalating doses until symptom control, with phenobarbital added when maximum dose was achieved. Phenobarbital was discontinued before weaning took place. A second cohort of 24 infants was enrolled with the same design, but modifications included higher initial and maximum dose, and an increased rate of uptitration of dose (25% vs 20%).[40] Both this trial and a subsequent double blind, double dummy, single site, randomized controlled trial (BBORN— **B**linded **B**uprenorphine **or** Neonatal **M**orphine Solution) demonstrated significant reductions

in length of stay and length of hospitalization.[41] The BBORN treatment regimen differed from the open label cohorts in a more aggressive morphine up-titration (20% vs 10%) and a parallel weaning of phenobarbital and opioid in both arms. Across all published prospective trials, 11 buprenorphine and 9 morphine-treated infants required phenobarbital adjunctive therapy due to inadequate control of symptoms with opioid alone. A small unpublished cohort of 11 infants with concomitant benzodiazepine exposure has enrolled using the same regimen as the BBORN trial.

Hall reported results from a cohort of buprenorphine treated infants compared to standard of care methadone.[42] Phenobarbital was added if maximum dose of buprenorphine was reached or if weaning was not achieved after 24-48. Phenobarbital was continued after the opioid was weaned off, and some infants were discharged to home on phenobarbital. The weaning protocol also differed from that in the clinical trials described above. (Table 2) Though treatment selection (buprenorphine or methadone) was not randomized, the demographics characteristics of the two groups of infants were similar. Opioid treatment duration and length of stay was less than was seen in the clinical trial cohorts described by Kraft, but the magnitude of the reduction on each measure was similar. A large follow-up cohort study from Hall using a slightly modified buprenorphine and adjunct regimen demonstrated a similar reduction in length of opioid treatment.[43]

Buprenorphine Safety

Buprenorphine has a favorable safety profile in adults for respiratory depression compared to full mu opioid agonists. Deaths from buprenorphine overdose are uncommon in adults, unless there is concomitant use of alcohol, benzodiazepine, or other hypnotics. With increasing doses there is a ceiling phenomenon after which there is minimal change in pharmacodynamic effects, which may be due to partial agonism. This favorable effect on respiratory depression explains the three fold lower rate of overdose while on methadone treatment compared to buprenorphine.[44] Though generally responding

well with overdose, children under three years appear more susceptible to respiratory depression than adults.[45-46] The buprenorphine exposure response relationship varies with specific pharmacodynamic endpoint measured, but for respiratory rate depression the plateau occurs at 16 mg of sublingual solution in adult, opioid naïve subjects. This dose is associated with a Cmax of ~10 ng/ml.[47] Recent investigations confirm that the ceiling effect is pharmacodynamic and not pharmacokinetic, as there is linear dose to exposure relationship, with serum concentration of >170 ng/ml well tolerated in opioid experienced volunteers.[34] In adults, the arrhythmogenicity of methadone also likely increases morbidity relative to buprenorphine. In adult population studies, buprenorphine has a 10 fold lower incidence of arrhythmia than methadone,[48] due likely to less of a propensity QT prolongation.[49] This favorable profile is maintained in adolescents.[50] No arrhythmia adverse event reports for patients under age 18 have been submitted to the FDA.[51]

Pharmacologic treatment of NAS with morphine or methadone in a monitored inpatient setting is safe and well tolerated. Clinical experience with buprenorphine has been similarly favorable. In published clinical trials of NAS, there have been have been three serious adverse events. The second patient randomized to buprenorphine developed generalized seizures 78 hours after the initial dose but there was no causal link of under-treatment of withdrawal or a dose dependent effect of buprenorphine. Post event evaluation revealed normal serum laboratory and lumbar puncture indices, and negative cultures. An interictal EEG was negative and MRI of the brain revealed a small amount of dependent subdural hemorrhage within the posterior fossa likely related to the birthing process and deemed unlikely to be pathogenic, with no parenchymal abnormalities. At one-year follow up, the child was developmentally normal and seizure-free. Other serious adverse events in the clinical trials included CMV infection and supraglottoplasty associated with the Pierre Robin syndrome, both of which were extant prior to buprenorphine exposure. Hall did not identify any safety issues associated with buprenorphine in his

cohort of use in a treatment paradigm.[42] Elevated tranaminases have been noted in adult cohorts treated with buprenorphine. Liver functions were monitored during NAS clinical trials without any elevations, consistent with a lack of signal in adolescents[52] and pediatric overdose patients.[46]

Buprenorphine PK/PD in NAS

The first published description of buprenorphine in neonates consisted of a single intravenous study by D.A. Barrett in critically ill premature infants requiring pain control.[53] This trial used a radioimmune assay, which differed from subsequent studies. Mean concentration at steady state was 4.3 ng/ml. Clearance and Vd were low, and postinfusion terminal sampling demonstrated a half life of 20 hours. (Table 3) Phase 1 and 3 clinical trials in NAS sublingual administration had collection of PK samples assayed using liquid chromatography–tandem mass spectrometry optimized for small sample volume,[54] from which a population PK model was generated.[55] Initial attempts using only the phase 1 infant data did not construct a reasonable model, and thus rich adult volunteer data was used to supplement the model with a final use of (n=209) from 24 neonates and from 5 healthy male volunteers (n=94). The model identified weight and post natal age as the most important covariates in determining apparent clearance of buprenorphine. These, however, only explained 5% of intra-individual variability of clearance. Mean clearance in the studied population (mean weight 3 kg and age of 5 days) was 3.5 L/hr/kg, which is consistent the adult range of 1.3-3.2 L/hr/kg. There were significant developmental effects, with a model predicted clearance that rose quickly with age, reaching 50% of adult values at 0.5 days and 90% by 10 days.(Figures 1 and 2) Concomitant phenobarbital dosing did not impact buprenorphine PK, but the number of infants driving this observation was small. Data from the phase 3 BBORN trial based upon this structural model revealed similar results to that seen in the phase 1 trial.[56] Kamatkar described the PK of buprenorphine in 63 samples from a cohort of 20 NAS infants treated at the University of Cincinnati in an open label approach. A one compartment model with Bayesian

estimates of individual PK parameters was used. [57] In all published models of buprenorphine in NAS, interindividual variability was high. The lack of dense sampling close to a dose and lack of concomitant IV administration limit full characterization of adoption kinetics. A possible source of variability is the relative fraction of dose absorbed through the sublingual route. In adults, the bioavailability of a swallowed dose is low due to high first pass metabolism. The hepatic extraction ratio approaches 1 in adults.[33] It is unknown if this applies in neonates for a number of reasons. Buprenorphine is metabolized primarily by CYP 3A4.[58] Total 3A4 activity, as measured by cisapride probes, is substantially reduced in neonates.[59] The duodenal expression of 3A4 protein and metabolic activity as measured by 6β-hydroxytestosterone formation, are markedly decreased in the neonatal population.[60] Both CYP 3A4 and p-glycoprotein expression are highly variable between individual children of the same age.[61] In addition, gut 3A4 expression or activity are poor predictors of systemic exposure of 3A4 substrates in pediatric patients. Fetal CYP 3A7 declines soon after birth, but is expressed during the first month of life during treatment for NAS. However, 3A7 has substantially less metabolic activity than 3A4/5 in the metabolism of buprenorphine metabolites. [62] Taken together, observations suggest a larger fraction of orally administered drug administered in neonates reaching the systemic circulation than in adults, which represents another potential source of interindividual variability. Intrainvidual variability may be impacted by sublingual dose administration. The mode of administration a solution under the tongue, followed by insertion of a pacifier. For volumes greater than 0.5 ml, the dose was split into two separated by 2 minutes. Assuming that infants have sizable first pass metabolism, variability in the relative fraction that is swallowed versus being retained in the sublingual fossa for at least two minutes could account for some dose to dose variability. The use of a q8 rather than longer interval dosing regimen was employed in anticipation of this potential source of variability, as well as providing greater ability to tailor individual dose changes based upon symptomatology.

Initial exposure response analysis suggests that buprenorphine concentration is the primary driver of control of withdrawal symptoms. This is supported by observations of 1) increased clearance associated with worse NAS symptoms, 2) more severe NAS generally requiring a higher AUC to control symptoms, and 3) that higher average concentrations of buprenorphine were correlated with faster time to stabilization.[56] Major covariates that drive this variability in drug exposure and clearance have not been identified. However, the linkage between exposure and response when combined with disease state models will allow future simulations to identify regimens more likely to control symptoms quickly and minimize duration of pharmacologic treatment.

Formulation

Current use of buprenorphine employs a 30% ethanolic solution which was chosen to mirror adult formulations, for which there was extant absorption data. This formulation is stable at room temperature for at least 30 days at room temperature and at 7 days in polypropylene dispensing syringes.[63] Additional advantages included microbiologic asepsis and simplicity of preparation in the context of a clinical trial. Ethanol does not decrease opioid withdrawal and is not expected to have provided any of the efficacy seen in NAS clinical trials. While ethanol is a common excipient in neonatal medications, including phenobarbital, formulations in neonatology should be in alcohol free vehicles where feasible. Consistent with prior observations that neonates clear ethanol faster than adults[64] infants receiving therapeutic buprenorphine had rapid fall in alcohol concentration between doses.[65] No values were above 70 mg/L, which is less than the American Academy of Pediatrics suggested limit of < 250 mg/L after a single dose.[66] Approximately a third of infants had a concentration above the European Medicines Agency lower suggested limit of 10 mg/L listed in the 2014 guidance, which still is in draft form. The model derived estimates are of a 7% bioavailability using this formulation in NAS patients.[55] At the current time there is no published report of a stable ethanol free buprenorphine

formulation. In addition to demonstration of shelf stability, an investigation of relative bioavailability would be needed to define comparative absorptive kinetics between a new and reference formulation before widespread use on NAS patients could be undertaken.

Future directions

Mirroring the state of neonatal therapeutics for many classes of medications, dose regimens for NAS were largely empiric following the spread of pharmacologic treatment for NAS in the 1970s. Clonidine was the first medication with generation of rich PK data.[67] While the PK of IV morphine pk in critically ill infants has been well characterized, similar data for oral administration data in NAS has only recently been described. [68] Methadone PK in NAS has been described.[69] The power of pharmacometric models is the ability to simulate dose regimens which can then be tested in patient populations. Model based simulation does not guarantee determination of the ideal dose, but is a clear advantage of the empiric and intuition-based approaches of dose selection commonly used. An elegant demonstration of this approach was implemented by Hall.[70] The methadone PKPD model generated from observational data[69] was used to simulate a new dose regimen. This was tested in a prospective fashion against the existing standard of care, leading to a reducing in length of stay.

The original dose of buprenorphine used in investigations of NAS was informed only by IV data in preterm infants coupled with relatively rich adult PK data. After the first cohort in the phase 1 study, a modest dose adjustment was made in starting and maximum doses, as well as uptitration rate. Broadly, simulation can help in defining an exposure response that could identify a target effective concentration. In the NAS population this appears to be ~ 0.8 ng/ml, which is comparable to adult estimates. Specific areas in which would benefit from dose optimization are time to stabilization of symptoms and the weaning regimen. It is not clear if obtaining control of symptoms earlier impacts the

duration of weaning, but reaching stabilization early without overshooting the proper dose would reduce duration of infant symptoms and reduce length of treatment. The weaning phase makes up the majority of time of treatment, so optimization of dosing in this period has the larger potential impact for reducing duration of treatment. Given the half-life and excellent safety profile, changing the dosing interval after stabilization from q8 to q12 or even q24 could facilitate transition to an outpatient setting.

Conclusion

Buprenorphine has demonstrated an efficacy advantage over standard opioid replacement therapy for NAS in both controlled clinical trials and treatment settings. Though the total number of treated patients in these cohorts is modest, consistency in effect size in different populations lends external validity to the findings. Buprenorphine is safe in NAS, and sublingual dosing has been demonstrated to be feasible in the neonatal population. Validation and testing of an ethanol-free formulation may encourage wider use. Pharmacometric analyses under development hold promise in defining exposure response relationships and optimization of dose regimens, including the potential for safely moving some of the weaning phases of treatment to the outpatient setting.

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Figure Legends

Figure 1: Model based developmental trajectory of neonatal post-natal age compared to adult clearance of buprenorphine.[55] PNA = post natal age

Figure 2: Model based developmental trajectory of neonatal post-natal age compared to adult peripheral volume (V_3) of buprenorphine.[55] PNA = post natal age