HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Clin Pharmacol Ther. 2018 January ; 103(1): 112–119. doi:10.1002/cpt.930.

Buprenorphine in Neonatal Abstinence Syndrome

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Abstract

Infants exposed *in utero* to opioids will demonstrate a withdrawal syndrome known as 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 the 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 that 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 the 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 nonspecific. While the bulk of morbidity and symptoms are due to withdrawal from 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 US Food and Drug Administration (FDA), advocate the 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.

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CONFLICT OF INTEREST

Dr. Kraft has served as an unpaid consultant to Chiesi Farmaceutici S.p.A.

Physician prescription of opioids occurs in 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, although a threshold exposure has not been established and maternal methadone dose is only weakly associated with neonatal symptoms.[8] Cardinal manifestations of neonatal opioid withdrawal are grouped into central nervous system (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. Nonpharmacologic treatments should be used in all infants with *in utero* exposure to opioids. There is no universal definition of what constitutes a nonpharmacologic treatment, but common measures include the infant rooming 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 nonpharmacological 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 coadministration 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, although results of a multicenter trial comparing methadone and morphine (NCT01958476) will provide some guidance between these two drugs. There is similarly no consensus of the role of adjunctive therapy. Differing regimens involve the addition of clonidine or phenobarbital at maximum dose of opioid, the use of either agent in parallel with the opioid, or as an opioid-free monotherapy. Phenobarbital is a more nonspecific CNS depressant and is believed to be particularly useful in poly-substance exposures, although there are theoretical concerns about neurotoxicity.[17] Clonidine has a mechanism more specific to opioid withdrawal and has a better evidence base of randomized trials, but it is used in 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 the Diagnostic and Statistical Manual of Mental Disorders,

Fifth Edition (DSM-5) as 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 ~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 the 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 appeared 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 more analogous pharmacodynamic endpoint in 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. The risk of relapse and patient substitution with illicit opioids following withdrawal of opioid replacement is high, and is an option only in highly selected cases with intense supervision.[22] Methadone has been the standard replacement opioid during pregnancy, with a recent increase in buprenorphine as the primary opioid. Based on three randomized controlled trials and 15 cohort trials, 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.[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 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 h in most infants, although there are occasional cases of more prolonged emergence of symptoms. Anxiety and depression incidence are higher in women with opioid use disorders,[27] so concomitant benzodiazepine[28] or antidepressant exposure[29] are common and can prolong the emergence time of symptoms.

BUPRENORPHINE PHARMACOKINETIC (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 that 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 bioavailability of 28–51%.[30,31] This occurs in 2–4 min, and longer retention times are not associated with increased systemic exposure.[30,32] Early publications and the product label of intravenous (i.v.) buprenorphine list a short elimination half-life. This is artifactual, due to lower sensitivity and nonspecificity of earlier radioimmune assays, along with a low therapeutic serum concentration due to the potency of buprenorphine.[33] Mean terminal elimination in adults after i.v. dosing of 2–16 mg with a sensitive assay was 25 ± 1 h with a volume of distribution of ~800 L.[34] Administration by the sublingual compared to i.v. 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 h. 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 are 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 PK predicts receptor occupancy reasonably well, and by linking to pharmacodynamic (PD) 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 another 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 be >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 I investigation was the first use of sublingual buprenorphine in NAS.[39] In the first cohort of 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 a 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 and a subsequent double-blind, double-dummy, single-site, randomized controlled trial (BBORN: Blinded Buprenorphine OR Neonatal morphine 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 uptitration (20% vs. 10%) and a parallel weaning of phenobarbital and opioid in

both arms. Across all published trials, 11 buprenorphine and nine 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 *et al.* reported results from a cohort of buprenorphine-treated infants compared to standard of care methadone.[42] Phenobarbital was added if a maximum dose of buprenorphine was reached or if weaning was not achieved after 24–48 h. 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). Although treatment selection (buprenorphine or methadone) was not randomized, the demographic 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 *et al.*,[39–41] but the magnitude of the reduction on each measure was similar. A large follow-up cohort 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 other full mu-opioid agonists. Deaths from buprenorphine are uncommon in adults, unless there is concomitant use of alcohol, benzodiazepine, or other hypnotics. Possibly due to partial agonism, with increasing doses there is a ceiling phenomenon after which there is minimal change in PD effects. This favorable effect on respiratory depression explains the 3-fold lower rate of overdose while on methadone treatment compared to buprenorphine.[44] Although generally responding well with overdose, children under 3 years appear more susceptible to respiratory depression than adults.[45,46] The buprenorphine exposure-response relationship varies with the specific PD 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 C_{max} of ~10 ng/mL.[47] Recent investigations confirm that the ceiling effect is pharmacodynamic and not pharmacokinetic, as there is a linear dose-to-exposure relationship, with serum concentrations 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] likely due to less of a propensity for 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 three serious adverse events. The second patient randomized to buprenorphine developed generalized seizures 78 h after the initial dose, but there was no causal link of undertreatment of withdrawal or a dose-dependent effect of buprenorphine. Postevent evaluation revealed normal serum laboratory and lumbar puncture indices, and negative cultures. An interictal EEG was negative and magnetic resonance imaging (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 1-year follow-up, the child was developmentally normal and seizure-free. Other serious adverse events in the clinical trials included cytomegalovirus (CMV) infection and supraglottoplasty associated with Pierre Robin syndrome, both of which were extant prior to buprenorphine exposure. Hall *et al.* did not identify any safety issues associated with buprenorphine in their cohort of use in a treatment paradigm.[42] Elevated transaminases 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 Barrett *et al.* 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 h (Table 3). Phase I and III clinical trials in NAS sublingual administration had a 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 I infant data did not construct a reasonable model, and thus rich adult volunteer data were used to supplement the model with a final use of (n = 209) from 24 neonates and from five healthy male volunteers (n = 94). The model identified weight and postnatal age as the most important covariates in determining apparent clearance of buprenorphine. These, however, only explained 5% of intraindividual 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, 2). Concomitant phenobarbital dosing did not impact buprenorphine PK, but the number of infants driving this observation was small. Data from the phase III BBORN trial based on this structural model revealed similar results to that seen in the phase I trial.[56] Kamatkar *et al.* 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. Published parameters were used in a one-compartment model with Bayesian estimates of individual PK parameters.[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 i.v. 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.[62] Taken together, the 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 inter-individual variability. Intraindividual variability may be impacted by sublingual dose administration. The mode of administration was 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 min. Assuming that infants have sizable first-pass metabolism, variability in the relative fraction that is swallowed vs. being retained in the sublingual fossa for at least 2 min could account for some dose-to-dose variability. The use of a q8 rather than a 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 on 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 has employed a 30% ethanolic solution, which was based on early work in adults. This was chosen primarily to mirror adult formulations, for which there was extant absorption data. This formulation is stable at room temperature for at least 30 days 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 a 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 suggested lower limit of 10 mg/L listed in the 2014 guidance, which is still 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 ethanol-free formulation of buprenorphine. 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 i.v. morphine 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 that 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 *et al*.[70] The methadone PK/PD 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 reduction in length of stay.

The original dose of buprenorphine used in investigations of NAS was informed only by i.v. data in preterm infants coupled with relatively rich adult PK data. After the first cohort in the phase I 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 that 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 the duration of infant symptoms and reduce the 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. Although 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.

Acknowledgments

Walter K. Kraft was supported by National Institute on Drug Abuse, R01 DA029076.

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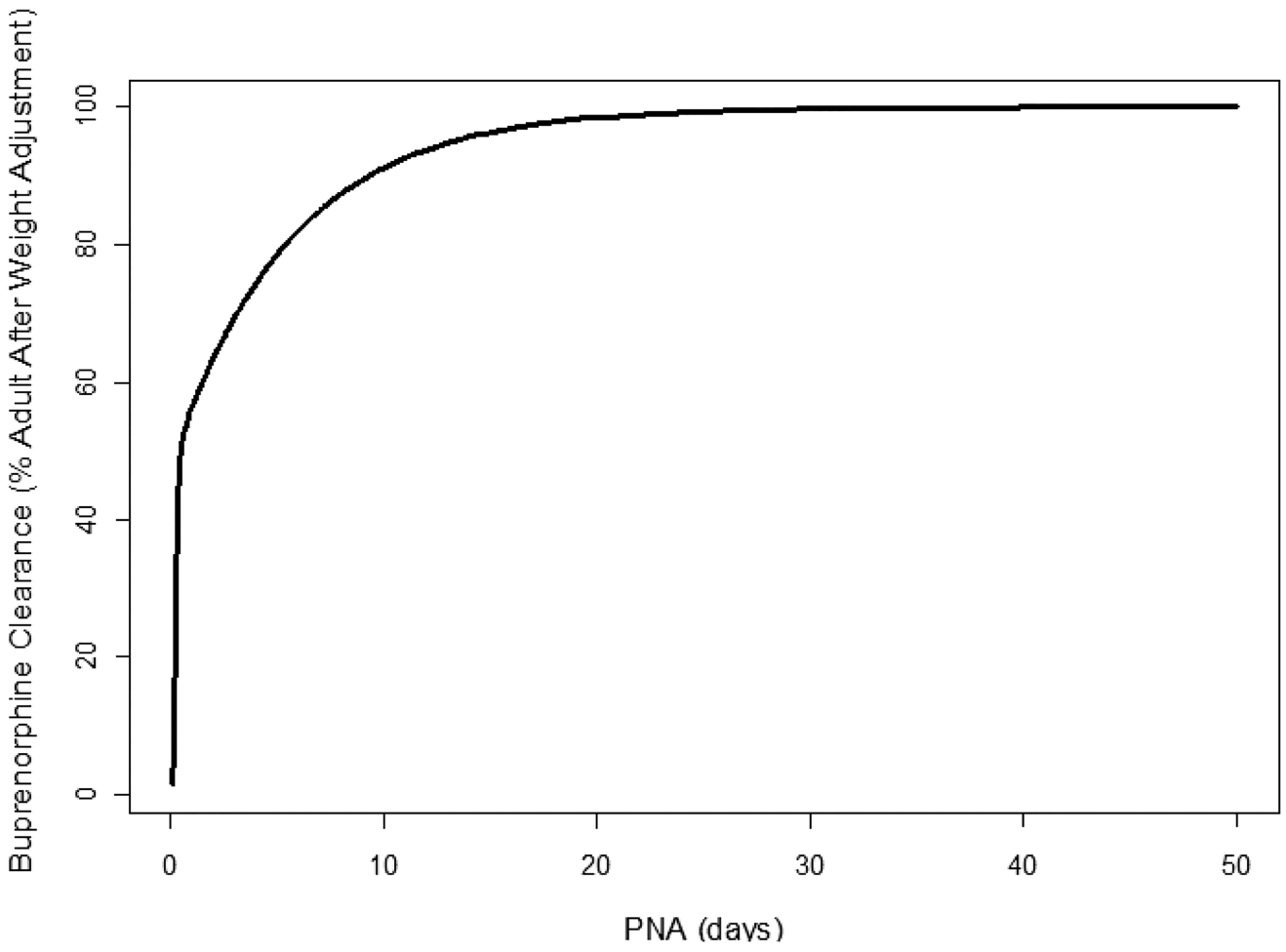

Figure 1.
Model-based developmental trajectory of neonatal postnatal age compared to adult clearance of buprenorphine.[55] PNA, postnatal age.

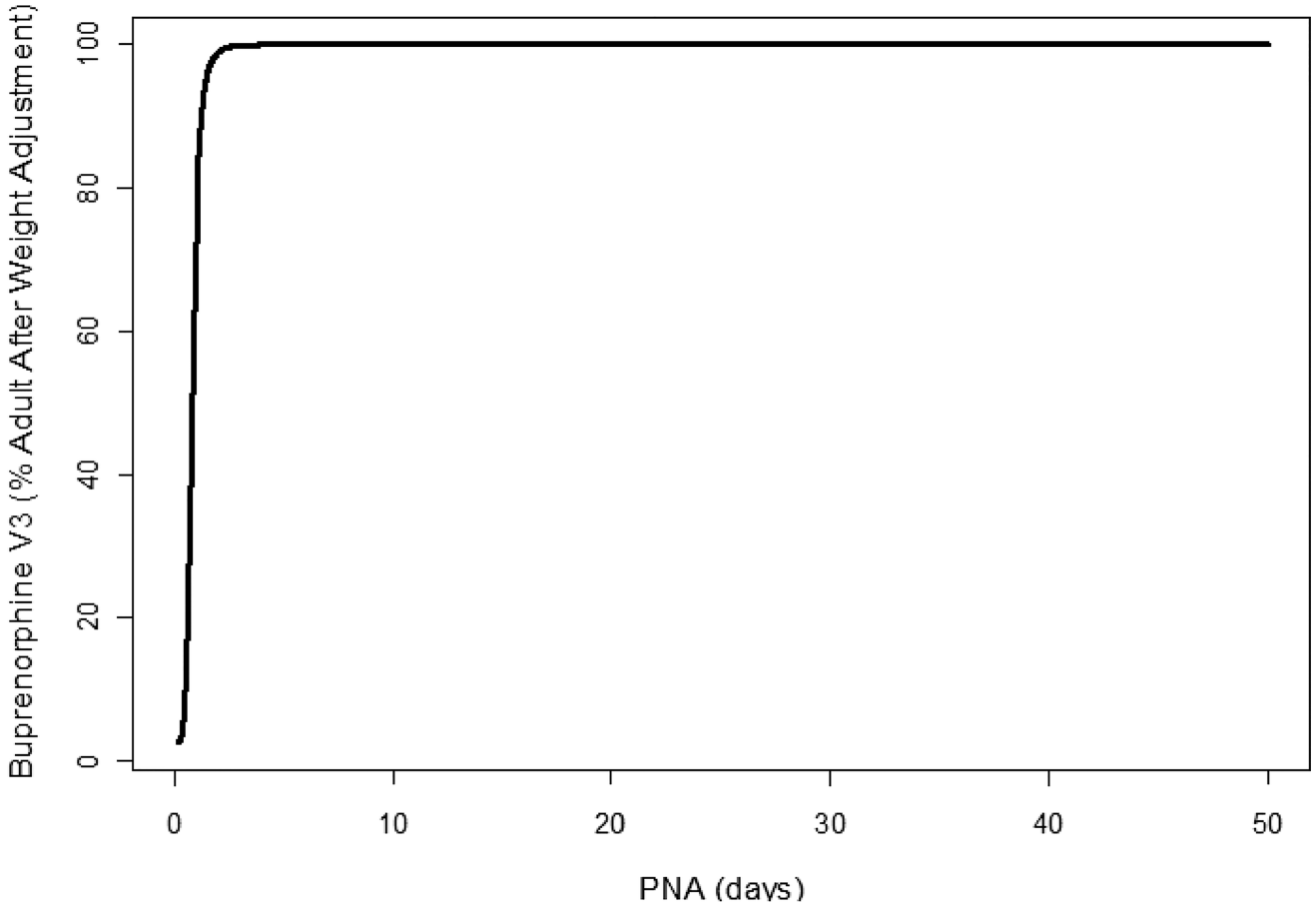

Figure 2.

Model-based developmental trajectory of neonatal postnatal age compared to adult peripheral volume (V_3) of buprenorphine.[55] PNA, postnatal age.

Table 1

Buprenorphine clinical experience in NAS

Study	Publication	Design	Buprenorphine			Comparator (*N*)	Reduction in length of treatment (days buprenorphine vs. comparator)
			N	Initial dose (μg/kg/day)	Maximum dose (μg/kg/day)		
Kraft[39]	2008	Open label, randomized	13	13.2	39	Morphine (13)	32% (22 vs. 32)
Kraft[40]	2011	Open label, randomized	12	15.3	60	Morphine (12)	39% (23 vs. 38)
Hall[42]	2016	Retrospective cohort	38	13.2	39	Methadone (163)	33% (9.3 vs. 14)
Hall[43]	2017	Retrospective cohort	174	13.5	22.5	Methadone or Morphine (186)	29% (7.4 vs. 10.4)
Kraft[41]	2017	Blinded, randomized	30	15.3	60	Morphine (33)	46% (15 vs. 28)
MOP Plus (NCT01671410)	Unpublished	Open label, randomized	6	15.3	60	Morphine (5)	N.A.

Table 2

Dose regimens of buprenorphine in NAS

	Kraft[41]	Hall[42]
Weight used for calculation of dose throughout treatment period	At time of drug initiation	Birth
Initial unit dose (μg/kg q8 hours)	5.3	4.4
Maximum unit dose (μg/kg q8 hours)	20	13
Up-titration rate	25%	0.8 μg/kg increments
Maximum # of up-titrations	6	11
Weaning rate	10%	0.8 μg/kg increments until 4.4 μg/kg, then fixed reduction in dose and interval
Cessation dose	Within 10% of starting dose	1.7 μg/kg q24
Add phenobarbital	At maximum buprenorphine dose	At maximum buprenorphine dose or unable to wean after 24–48 hr
Phenobarbital weaning	5 mg/kg reduced to 2.5 mg/kg after buprenorphine 50% of maximum dose; phenobarbital cessation after three additional down titration steps	Phenobarbital continued after buprenorphine stopped; dose weaned as an outpatient
Inpatient observation following cessation of last scheduled dose (hrs)	48	72

Table 3

Pharmacokinetic parameters of buprenorphine in NAS

	Model compartments	No. of infants	No. of samples	Route	Indication	Gestational age range (weeks)	Clearance (L/hr)	Vd (L)	Ka (hr^{-1})	$T_{1/2}$ (hr)
Barrett *et al.*[53]	One	12	N.A.	IV	Pain in prematurity	27–32	1.5	6.2	0.177	20
Ng *et al.*[55]	Two	24	209	SL	NAS	37–46	7.8	147	0.416	11
Kamatkar *et al.*[57]	One	20	63	SL	NAS	37–42	2.0	12.9	0.64	4.4
Moore *et al.*[56]	Two	28	172	SL	NAS	37–42	7.61	160	0.416	10

Ng *et al.* and Moore *et al.* values are based upon an adult model structure and simulated for a 3-kg, 5-day-old infant. Vd represents a pseudovolume (V2 + V3).