A randomised controlled trial of morphine versus phenobarbitone for neonatal abstinence syndrome

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Background: The incidence of neonatal abstinence syndrome (NAS) has increased 10-fold over the last decade in Glasgow. In the Princess Royal Maternity Hospital, it now accounts for 17% of special care baby unit (SCBU) admissions.

Objective: To compare opiate replacement therapy (morphine sulphate) with the present standard treatment (phenobarbitone) for management of NAS. The primary study end point was duration of pharmaceutical treatment. Secondary end points were the requirement for additional drugs and the requirement for SCBU admission.

Design: Double blind, randomised controlled clinical trial.

Methods: Differential diagnoses were excluded, and two consecutive Lipsitz scores > 4 defined NAS requiring treatment. Infants were randomised to receive morphine sulphate or phenobarbitone. Treatments were identical in appearance, odour, and volume. Increments, decrements, and discontinuation of treatments were protocol driven.

Results: Seventy five infants participated. All mothers received opiate replacement therapy (methadone) during pregnancy and most used other drugs (n = 62, 83%). No significant difference in maternal drug use patterns was observed between treatment groups. Median treatment duration was four days shorter with opiates (8 vs 12 days, Mann-Whitney U test, p = 0.02). Phenobarbitone treated infants tended to require second line treatment (47% vs 35%, \( \chi^2 \) test, p = 0.11) and SCBU admission (62% vs 30%, \( \chi^2 \) test, p = 0.04) more often.

Conclusions: Opiate replacement therapy appears to be superior for management of symptomatic NAS when maternal opiate use is prevalent. The shorter treatment duration and lower requirement for higher intensity nursing may have significant cost implications. Tailoring NAS treatment to local maternal drug use may result in similar benefits.

Neonatal abstinence syndrome (NAS) is a syndrome of drug withdrawal observed in infants delivered to mothers who are physically dependent on addictive drugs during their pregnancies, manifesting as non-specific symptoms and signs, of which irritability, poor feeding with an inadequate suck and high pitched crying are common. Rarely, seizures may occur and there is an increased neonatal mortality from sudden infant death syndrome in the short-term, in addition to a long term adverse neurodevelopmental outcome.

NAS is increasing in incidence worldwide. In the United States, the number of drug affected newborns has increased by 300% since the 1980s. In the United Kingdom, the incidence of drug exposed newborns varies between 14% and 90% of live-born infants, depending on the urban area and social class of the population sampled. More recently, anonymous screening of women attending antenatal clinics in London observed that 11–16% were using at least one illicit substance. In the area served by Glasgow Royal Maternity Hospital, NAS has increased 10-fold over the last decade, paralleling the increased usage of methadone as opiate substitution for pregnant mothers with a history of drug use. NAS at present accounts for 17% of admissions to the special care baby unit (SCBU). In addition, local audit suggests that symptomatic NAS has become increasingly difficult to treat, requiring multiple pharmaceutical treatments administered for longer durations. The increased prevalence of NAS has clear implications for mother-infant bonding, cot occupancy, nursing time, and costs.

Despite the increasing clinical burden of NAS, optimal management remains unclear as clinical trial evidence is insufficient. Conservative measures such as holding and minimal stimulation may suffice if symptoms are mild and non-progressive. However, more severe symptoms require adequate pharmacotherapy. Many pharmaceutical agents have been used historically to treat NAS, including clonidine, chloral hydrate, chlorpromazine, opioids, opiates, and phenobarbitone. In Studies to date can be criticised on their lack of standardisation of outcome measures, problems with randomisation, and failure to use a pre-evaluated scoring system to allow standardisation of the start of treatment, dosage alterations, and termination of pharmaceutical treatment.

The aim of this study was to compare the efficacy of initial treatment with an opiate versus phenobarbitone for infants with NAS caused by opiate withdrawal. The total duration of pharmaceutical treatment required to achieve symptom resolution was predefined as the primary study end point, and the requirement for higher intensity nursing in the SCBU or the need for an additional second line treatment as secondary end points.

Subjects and Methods

Phenobarbitone has been the standard first line treatment for symptomatic NAS at Glasgow Royal Maternity Hospital for many years. Oral morphine sulphate was selected as a treatment option for this study as opiates are the predominant class of drugs used by drug dependent pregnant women in Glasgow. Statistical advice was sought, and a sample size of 80 was estimated to detect a 0.5 SD difference in the total

Abbreviations: NAS, neonatal abstinence syndrome; SCBU, special care baby unit
duration of pharmacological treatment between the treat-
ment groups, assuming $\alpha = 0.05$. After informed written
parental consent had been obtained, infants with a history of
maternal drug use and two sequential scores of $> 4$ using
the Lipsitz tool was considered eligible for randomisation.
Alternative diagnoses for an irritable baby were excluded by
clinical examination and biochemical analysis (including
calcium, magnesium, and blood glucose concentrations). The
Lipsitz tool was selected as the measure of NAS severity as it
is the scoring system recommended by the American
Academy of Pediatrics, is less labour and time intensive than
alternative scoring systems in use, and has a sensitivity
approaching 80% for NAS requiring pharmaceutical treat-
ment when a score of $> 4$ is used. Six months before the
start of the study, all midwifery staff in both the postnatal
ward and SCBU were trained in its use and were well
accustomed to treatment alterations based on this score by
the time the study started. Case notes were also retro-
spectively reviewed to record Apgar scores at one and five
minutes, in case infant irritability reflected acute compro-
mise at the time of delivery. Infants were recruited on the
postnatal ward or after admission to SCBU if this was
required for any other reason such as prematurity. Local
clinical guidelines dictated that infants with NAS were
treated in the postnatal ward with their mothers unless they
required nasogastric feeds, had severe withdrawal, were
admitted to SCBU for another reason such as prematurity/
sepsis, or their mothers had already been discharged on the
10th postnatal day. Seventy six infants with symptomatic
NAS fulfilling the above criteria were eligible for recruitment
permission was refused for one infant, so 75 infants were
recruited. Table 1 summarises the clinical characteristics of
those studied.

Infants were randomised to receive morphine sulphate
or phenobarbitone orally, labelled as substance A and sub-
stance B respectively. Randomisation was performed using a
computer generated random number technique. Morphine
sulphate was prescribed in a dose of 50 $\mu$g/kg and pheno-
obarbitone in a dose of 2 mg/kg. Both drugs were adminis-
tered four times a day as identical colourless and odourless
solutions of equal volume. Solutions A and B were speci-
cifically prepared for this study by Tayside Pharmaceuticals,
Ninewells Hospital, Dundee, Scotland, UK. Throughout the
study period, all staff involved remained unaware of the
identity of either treatment. To ensure objectivity, the start,
dosage increments and decrements, and eventual termina-
tion of treatment were protocol driven (fig 1) based on
sequential 12 hourly postprandial Lipsitz scores, which were
obtained throughout the period of study. The start and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oramorph (n = 41)</th>
<th>Phenobarbitone (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>40 (32–42)</td>
<td>39 (33–41)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2940 (1760–3930)</td>
<td>2780 (1860–3760)</td>
</tr>
<tr>
<td>Age randomised</td>
<td>48 (12–240)</td>
<td>48 (12–240)</td>
</tr>
<tr>
<td>Breast fed (%)</td>
<td>4.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Methadone dose (mg)</td>
<td>30 (5–65)</td>
<td>35 (10–100)</td>
</tr>
<tr>
<td>Interaquartile range</td>
<td>15–49</td>
<td>24–51</td>
</tr>
<tr>
<td>Opiate exposed (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Benzodiazepine exposed (%)</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>Exposed to other drug classes (%)</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Apgar 1 minute</td>
<td>9 (6–10)</td>
<td>9 (4–9)</td>
</tr>
<tr>
<td>Apgar 5 minutes</td>
<td>10 (8–10)</td>
<td>9 (6–10)</td>
</tr>
</tbody>
</table>

Where applicable, values are mean (range)

Statistical analysis was performed using SPSS for Windows
(SPSS Inc, Chicago, Illinois, USA). The relation between
demographic factors and the primary outcome variable (total
duration of pharmaceutical treatment) was examined initial-
ly using non-parametric tests. Demographic factors corre-
lating with the primary outcome were entered into a uni-
ivariate linear model (general linear modelling, analysis of
covariance) to account for potential confounding influ-
ences. This technique was used to determine the independent
influence of the treatment allocation (A or B) on the duration
of pharmaceutical treatment. The model used included
treatment allocation and use of other non-opiate based drugs
as between subjects factors, and the maternal methadone
dose as a covariate, as these correlated significantly with the
primary outcome. For the secondary outcome analyses
(required for second line treatment, admission to SCBU
required), non-parametric tests were used to determine which
factors and covariates influenced these outcomes.

**RESULTS**

**Drugs misused by mothers**

All mothers of the infants in this study were using metha-
done as part of a harm reduction policy. Table 1 summarises
the classes of drugs that infants were exposed to in utero.
No significant differences were observed between those
randomised to either treatment group (morphine sulphate/
phenobarbitone) in the dose of methadone used by mothers
during their pregnancy. Most mothers used other drugs in
addition to the methadone substitution provided during
pregnancy ($n = 62, 82.7%$). The other classes of drugs used
by mothers were predominantly benzodiazepines and a
variety of others, which included antidepressants, neurole-
ptics, and cannabis. Cocaine use was uncommon. Table 1 sum-
marises the proportions of infants exposed in utero to these
other classes of drugs. Infants randomly allocated to receive
phenobarbitone tended to have been exposed to benzo diaz-
epines and other classes of drugs more often than those
randomly allocated to receive morphine sulphate.

**Effect of treatment allocation on study outcomes**

The primary outcome measure was the duration of pharma-
ceutical treatment required to objectively resolve the symp-
toms of NAS. Infants randomised to receive morphine sul-
phate required a median of four fewer days active treatment
than those allocated to phenobarbitone ($8 \times 12$ days, Mann-
Whitney, $p = 0.02$). Maternal methadone dose (Spearman’s
$r = 0.24$, $p = 0.04$) and classes of drugs used other than
opiates ($r = 0.24$, $p = 0.41$) also correlated with total days
receiving treatment. When these significant influences were
accounted for using linear modelling (analysis of covariation),
treatment allocation remained a significant independent
predictor of the total duration of pharmaceutical treatment
($p = 0.03$). Maternal methadone dose also independently
influenced the duration of treatment ($p = 0.04$), although
the use of other classes of drugs did not.

Secondary outcome measures were the requirement for an
additional second line treatment to adequately suppress
symptoms of NAS (chloral hydrate 15 mg/kg), and the
requirement for admission to the SCBU. Infants receiving
phenobarbitone as their primary treatment tended to require
an additional drug more often to suppress NAS symptoms
($47% \times 35%$, $\chi^2$ test $p = 0.11$). Other factors also appeared to
correlate with the requirement for second line treatment. These included the reported maternal methadone dose (r = 0.32, p < 0.01), in utero exposure to classes of drugs other than opiates or benzodiazepines (r = 0.27, p = 0.02), and exposure to benzodiazepines (r = 0.24, p = 0.04). To determine the independent effect of treatment allocation on the requirement for second line therapy, logistic regression was used. Treatment allocation did not independently predict the requirement for second line therapy (p = 0.34), which was only significantly predicted by maternal methadone dose (p = 0.02).

The requirement for admission to SCBU, a subjective surrogate marker of more severe drug withdrawal, appeared to be lower in infants who received morphine sulphate as their primary treatment (30% vs 62%, x^2 test p = 0.04). However, other factors also appeared to correlate with the requirement for SCBU admission. These included the reported maternal methadone dose (p = 0.27, p = 0.02), exposure to classes of drug other than opiates or benzodiazepines in utero (p = 0.27, p = 0.02), and the treatment allocated (p = 0.27, p = 0.02). The treatment allocated (morphine sulphate/phenobarbitone) independently predicted the requirement for SCBU admission (p = 0.04) as did the maternal methadone dose (p = 0.04). However, the duration of SCBU stay was not predicted by any of the above factors.

**DISCUSSION**

In this study, tailoring the treatment for symptomatic NAS to match the local pattern of maternal drug use was associated with two important benefits: (a) a more rapid resolution of the symptoms and signs of NAS, such that treatment was required for a shorter time; (b) a significantly reduced requirement for higher intensity nursing, implying more effective treatment. These two benefits are likely to translate into reductions in cot occupancy (estimated at about 300 cot days per annum, based on 80 cases of NAS per annum in our centre) and midwifery staff time. Both will have considerable cost implications. However, to replicate these findings it is important to understand local maternal drug use.

Data comparing the use of opiates with other agents to treat symptomatic NAS are limited. Pacifico et al. concluded that morphine alone was superior to the combination of phenobarbitone and diazepam, and to the combination of morphine, phenobarbitone, and diazepam. Unfortunately, the report contains insufficient detail on its study design to be easily compared with our study. Madden et al. found no significant difference between treatments consisting of methadone, phenobarbitone, or diazepam, although treatment decisions were made subjectively without the aid of a standardised chart, which introduces the possibility of bias. Few studies are directly comparable with our findings.

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**Figure 1** Flow chart summarising the study protocol for start, discontinuation, and dosage adjustment of treatments. NAS, Neonatal abstinence syndrome; TBG, true blood glucose; Rx, prescription; U+E, urea and electrolytes.
In this study, several weaknesses must be noted. No loading dose of phenobarbitone was used to ensure that the drug regimens were blinded. This could potentially have introduced bias in favour of morphine sulphate. However, the necessity of phenobarbitone loading is debatable. Kaltenbach et al. compared 36 drug-exposed infants treated with phenobarbitone regimens that did or did not use a loading dose. No significant difference was identified between regimens. However, Finnegar et al. observed a significantly reduced time to symptom control in infants receiving a loading dose of phenobarbitone. We acknowledge that the lack of a loading dose of phenobarbitone in our study may have contributed to the apparently poorer treatment outcomes in the phenobarbitone group.

In addition, our protocol did not allow for adjustments in either the frequency or dose of the allocated treatment. Kendall compared phenobarbitone with three hourly treatment with paregoric (an opiate based drug) and observed no difference in the treatment duration required. Kho observed enrolled infants to treatment with morphine every four to six hours or phenobarbitone (loading dose and daily maintenance thereafter), but the methodology does not allow comparison with our randomised trial. The optimal frequency of opiate dosing for symptomatic NAS remains unclear. However, the dose of opiate administered in this study may be of more importance. Maternal methadone dose was an independent predictor of the duration of NAS treatment required, the requirement for second line treatment, and the requirement for SCBU admission (a subjective surrogate of severity of the withdrawal process). These observations suggest that the morphine sulphate dose used may have been insufficient, and therefore the benefits of opiate replacement therapy for symptomatic NAS may have been underestimated. Dobierzak et al. observed that the maternal methadone dose at delivery correlated significantly with the neonatal plasma methadone concentration on day 1 of life, the severity of central nervous system signs of withdrawal, and the rate of decline of the neonatal plasma methadone concentration from day 1 to day 4 of life. Further work is planned locally to investigate whether a higher dose of opiate replacement for symptomatic NAS, particularly for infants whose mothers were receiving large methadone maintenance doses, has additional clinical benefit above that observed in this study.

In interpreting the findings, it is important to note that differences were reported in the pattern of use of other drugs (benzodiazepines and other classes) between those randomly allocated to receive either morphine sulphate or phenobarbitone, with the phenobarbitone group exposed significantly more often to benzodiazepines (44% v 22%) and tending to have been exposed more often to other classes of drugs (23% v 10%). However, when statistical methods that adjusted for these differences were used (linear modelling, logistic regression), in utero exposure to benzodiazepines and other classes of drugs did not appear to independently influence any of the predefined study outcomes. This implies that the differences observed in the maternal use of these other drugs were not of great clinical importance to the outcome of the present study. We recorded the maternal drug history, but did not perform further analytical techniques to validate it. Modern analytical techniques such as meconium analysis\(^\text{12,13}\) may have allowed a more definitive estimation of in utero drug exposure.

The aims of this study were confined to inpatient outcomes within the neonatal period. Exploration of the long term neurodevelopmental effects of the study protocol (randomisation of infants to receive either phenobarbitone or morphine sulphate) was not its purpose, and the long term morbidity from neonatal drug withdrawal remains relatively unstudied. Few studies have followed drug exposed children beyond the first few years of life, as confounding variables, such as environment and dysfunctional caregivers, make it extremely difficult to determine the causes of differences in ability. It is hoped to address this lack of long term data by re-examining at primary school age the present cohort and an environmentally matched control group not exposed to drugs, with a battery of cognitive ability tests as the primary outcome.

In conclusion, this study suggests that opiate replacement therapy for symptomatic NAS can achieve meaningful clinical benefits in a population in which maternal use of drugs from the opiate class is predominant. This policy more effectively suppressed the underlying disease process of NAS, thereby reducing the time to achieve adequate symptom control. Further studies are required to determine the optimal regimen and dose, and meconium analysis\(^\text{15,16}\) may be useful for tailoring the clinical management of these infants and may give further information on whether in utero polydrug exposure is of clinical importance. The potential benefit of long acting opiates (such as methadone) that can be administered from time to time requires exploration, as an opportunity for domiciliary pharmaceutical treatment may exist. These thoughts for the future will require formal clinical assessment in a randomised clinical trial.

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REFERENCES


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