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REGULAR ARTICLE

Comparison of chlorpromazine versus morphine hydrochloride for treatment of neonatal abstinence syndrome

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Abstract

Aim: To compare the duration of treatment for neonatal abstinence syndrome (NAS) using chlorpromazine versus morphine hydrochloride.

Methods: We compared two case series of term infants with NAS treated with either morphine hydrochloride (MH) or chlorpromazine (CP). Seventeen infants were treated with MH from 1998 to 1999, and 20 infants were managed with CP from 2000 to 2001. The duration of treatment was compared, and multivariate analysis was used to identify independent risk factors related to the duration of treatment.

Results: Characteristics of the mothers (duration of drug addiction, abuse of other substances) and infants (birth weight, proportion breastfed) were similar in the two groups. The mean duration of CP treatment was 6 days (range 3.5–9 days), significantly fewer days than with MH treatment, which was 16 days (range 10–21 days; $p < 0.001$). There were fewer hospitalization days (11 days; range 9–14 days) for CP treatment compared with MH-treated infants (18 days; range 16–25 days). Treatment with CP was independently associated with shorter hospitalization time.

Conclusion: CP appears to shorten the duration of NAS compared with MH. Larger prospective randomized trials are needed to confirm our findings.

INTRODUCTION

Neonatal abstinence syndrome (NAS) occurs in 48% to 94% of children born to mothers who use opiates (1). There is currently no international consensus concerning the optimal medical management of NAS, which requires medical and supportive therapy (2). For opioid-related NAS, morphine hydrochloride (MH), paregoric elixir, morphine sulphate, tincture of opium and methadone are given as substitutes. Nonmorphine treatments such as phenobarbital, chlorpromazine (CP), diazepam and clonidine provide symptomatic relief (3–6). In the United Kingdom, CP for NAS is prescribed more often than opiates (71% vs. 11%) (5). In contrast, in the United States, morphine group agents (morphine solution or tincture of opium) are given to 63% of children born to mothers who are dependent on opiates (2,7). As recommended by the French Pregnancy and Addictions Study Group, MH was used as first-line therapy in our unit before the year 2000 (8), but we observed that the hospitalization time was long (i.e. >10 days). We therefore began using CP, which is widely used in United Kingdom (5). After the transition to using CP in 2000, we observed a reduction in the duration of hospitalization.

The objective of this exploratory study was to compare the duration of treatment using CP versus MH for infants with NAS.

METHODS

Between 1998 and 2001, all mothers of neonates hospitalized for NAS monitoring in the Mother–Child Unit at the University Hospital in Montpellier were evaluated for inclusion in our study. The study included mothers followed at the Mother–Child Unit for pregnant addicted patients at the university hospital in Montpellier and their singleton term and near-term infants with a gestational age longer than 36 weeks and birth weight greater than 1900 g. Infants with life-threatening diseases or severe congenital malformations were excluded.

For each mother and baby, we collected data that included the mother's age at childbirth, the infant's age at the beginning of treatment for NAS and the Finnegan score (9). As the mothers were followed over a few months while at our institution, they were queried using a prospective standardized questionnaire about the dose, duration and frequency of the substances they used during pregnancy. We specifically queried them about their use of opiates, benzodiazepines, cocaine, ecstasy (MDMA, 3,4 methylene dioxymethamphetamine), amphetamines, cannabis, alcohol and tobacco. The severity of their drug addiction was evaluated using the Toxicomanie Médico-Socio-Psychologique (TMSP) score (10). Infants were considered to be small for their gestational age when their birth weight was below the

third percentile for their gestational age (11); these subjects were included in our analysis. We also collected data from subjects who required supportive therapy rather than medical treatment.

We measured NAS scores using the Finnegan scale (9). All infants were scored at 3- to 4-h intervals, depending on the organization of nursing care. When the NAS score was above 8, supportive care was optimized. If three consecutive scores were above 8, pharmacological treatment was initiated. The starting dose of MH (0.2 mg/mL morphine) was 0.3 mL/kg every 4 h. The starting dosage of CP (1 mg/drop) was two drops/kg per day every 8 h (12); CP was a 4% drinkable solution (Largactil® Sanofi-Aventis, France).

The dosage of MH was increased by 0.1 mL/kg every 4 h if the NAS score was between 11 and 13, and by 0.2 mL/kg every 4 h if the score was between 14 and 16. For CP, the dosage was increased by one drop every 8 h if the score was between 11 and 13, and by two drops every 8 h if the score was between 14 and 16.

NAS was considered to be controlled after three consecutive scores were ≤ 8 over a 12-h period. After NAS was controlled, the infants were scored every 6 to 8 h.

Weaning was initiated after a neonate was maintained on a stable dosage for 48 h. Medication was reduced in neonates if every score was below 8 for 24 h. If scores were ≥ 8 at any time on the day medication reduction was initiated, weaning was deferred. CM was reduced by 0.3 mL/kg per day, and CP was reduced by one drop per day. If three consecutive scores were below 4, CM was reduced by 0.6 mL/kg per day, and CP was reduced by two drops per day. Hospital discharge was allowed 2 days after treatment was stopped.

Caregivers and parents provided supportive therapy to reduce environmental stimuli such as noise, light and number of visitors. Caregivers soothed neonates with slow rocking, swaddling, by holding them firmly in the foetal position, with skin to skin contact and using nonnutritive sucking (13). This practice of nonpharmacological therapy has been standardized in the mother–child unit since 1997, and all nurses working in the unit have been using this care for years. Nurses were trained to perform Finnegan scoring and to make therapy decisions.

Statistical analysis

The primary outcome was duration of CP or MH treatment. We also explored hospitalization duration as a secondary outcome. For continuous variables, descriptive statistics and medians (first quartile and third quartiles) were estimated unless otherwise indicated. The relationship between treatment duration and baseline risk factors was evaluated with chi-square statistics or Fisher's exact test (when numbers were small). The relationship between outcomes and factors that were not normally distributed was evaluated using the Mann–Whitney test for independent samples or using Kruskal–Wallis tests for multiple measurements. For smaller samples with multiple comparisons, we used a Bonferroni correction for conservative significance testing. To identify factors independently associated with treatment duration, unadjusted variables with a p-value less than 0.2 were used in multiple linear regressions. We also used clinically relevant variables, such as the number of drugs used during pregnancy, exclusive breastfeeding and a history of dependency. Independent variables were selected in a stepwise linear regression analysis. We used the coefficient of determination (R) to quantify the proportion of variance and to evaluate the adequacy of the model. Regression coefficients and 95% confidence intervals (CI) were also estimated. Statistical significance was defined by an alpha level of 0.05. All statistical analysis was generated using SAS/STAT software, Version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Between August 1998 and the December 2001, there were 8620 live births at the Arnaud de Villeneuve hospital. All subjects except one had a gestational age (GA) $\geq$ 37 weeks; one had a GA of 36 weeks and 5 days. Of the 59 singletons (52% female) who met the inclusion criteria, 47 (80%) presented with NAS. The majority of infants presenting with NAS (37/47; 79%) required medical treatment; the others were successfully managed with supportive care. Among the 37 medically treated infants, 17 were born between 1998 and 1999 and treated with MH. The 20 infants born during the following 2 years, 2000 to 2001, were treated with CP. The baseline characteristics of the mothers and the children were similar in both groups; more mothers received methadone in the CP group, but the difference was not statistically significant (Table 1). The TMSP score was similar in all mothers. Onset of NAS occurred at a mean postnatal age of 27 h (range 6–48 h). Scores were higher in the CP group compared to the MH group (Table 2). A significant postnatal weight loss (more than 10% birth weight) tended to be more frequent in the CP group (Table 2).

Infants given CP had significantly shorter duration of treatment (6 days; range 3.5–9 days) compared to those given MH (16 days; range 10–21 days; $p < 0.001$). The duration of the hospital stay was also shorter for the CP group (11.5 days; range 9–14 days) than for the MH group (18 days; range 16–25 days; $p < 0.001$) (Table 2). Subjects who did not need medical treatment were hospitalized, on average, for 7.5 days (range 6–10 days). Variables that were included in the linear regression model included NAS medication, postnatal age when NAS treatment was initiated, age of the mother at childbirth, the maximum Finnegan score, the number of drugs used during pregnancy, exclusive breastfeeding and history of dependency. The type of NAS treatment was the only independent variable associated with duration of treatment, with an average difference of 9 days (95% CI 5–13). The coefficient of determination for the model was $R = 42\%$.

DISCUSSION

We observed a significant reduction in duration of treatment and hospitalization for subjects with NAS treated with CP versus MH. The duration of CP and MH treatment observed in our study was in agreement with previously published

Table 1 Characteristics of mothers and their infants treated with morphine hydrochloride (MH) or chlorpromazine (CP)

Variable	MH (n = 17)	CP (n = 20)	p-value
Age of mother, years	30 [27–33]	32.5 [29–34.5]	0.22
Pregnancies, n	3 [2–4]	3 [2–4]	0.74
Parity, n	2 [1–2]	2 [1–3]	0.83
Vaginal delivery	71	60	1
History of dependency, years	9.5 [4–14]	11 [9–12]	0.37
Dependence on buprenorphine, %	76.5	60	0.29
Dependence on methadone, %	11.8	35	0.14
Smoking, %	94	95	0.46
Abuse of more than 2 other substances*, %	18	10	0.64
Abuse of benzodiazepines, %	41	35	0.70
Abuse of cocaine, %	23.5	20	1
Abuse of cannabis, %	41.2	25	0.29
Gestational age at birth, weeks	40 [39–41.5]	40 [39–41]	0.82
Birth weight, g	2900 [2680–3550]	2960 [2640 –3285]	0.62
Small for gestational age, %	12	15	1
Exclusive breast feeding at discharge, %	29	36	1

Values are expressed as the median [P25–P75] or as percentiles.
*Benzodiazepines, cannabis, cocaine, ecstasy, amphetamines, alcohol, heroin.
No significant differences between groups MH and CP.

Table 2 Characteristics of NAS and NAS treatment in infants given morphine hydrochloride (MH) or chlorpromazine (CP)

Variable	MH (n = 17)	CP (n = 20)	p-value
Postnatal age at first signs of NAS, h	25 [21–47.5]	40.5 [24–55.5]	0.27
Maximum NAS score, value	12 [11–14]	13 [12–15]	0.03
Weight loss, g	180 [130–250]	260 [175–315]	0.12
Loss of more than 10% of birth weight %	13	25	0.67
Postnatal age at initiation of medication, h	55 [32–96]	77 [67–107]	0.04
Duration of medical treatment, days	16 [10–21]	6 [3.5–9]	< 0.001
Duration of hospitalization, days	18 [16–25]	11 [9–14]	< 0.001

Values are expressed as the median [P25–P75] or as percentiles.

data (14–16), but to our knowledge, there are no published studies comparing CP and MH in the treatment of NAS.

Although the number of subjects was small in our study, we observed a statistically significant and clinically relevant difference in duration of treatment between neonates treated with CP compared with those receiving MH. This result is consistent with the pharmacokinetic profiles and mechanisms of action of CP and MH. Plasma levels of CP peak more rapidly than levels of MH (2.8 h vs. 5 h, respectively) and CP has a longer half-life (30 h vs. 1.5–4.5 h) due to strong plasma protein binding (90–99% vs. 30–35%) (17).

A study bias is possible since the choice of medication was not random, but depended on treatment date. For example, the initiation of treatment occurred later during the second period (CP) than during the first period (MH). Development of NAS depends on drug exposure in the mother (18,19), and this difference in initiation of treatment could be related to the higher proportion of mothers treated with methadone during the second period (35% vs. 11.8%). In addition, the significant reduction of NAS duration during the second period could be related to changes in supportive NAS care during this time. This latter possibility is unlikely, since the study was performed in a single unit over a relatively short period without significant changes in the supportive care. For the same reason, the NAS score was the same over the two time periods, since there was no significant variation in nurse practices before and after the introduction of CP.

We know of no reported adverse effects in neonates treated with CP for the short period of time associated with NAS treatment (20). Although we found no adverse effects, the retrospective nature of our study precludes any conclusions about how well CP is tolerated. The American Academy of Pediatrics suggests limited use of CP in the treatment of NAS because of potential haematological and neurological risks (7). However, no adverse events have yet been reported. A study of 50 premature and full-term neonates

that received 2.8 mg/kg CP per day in four doses reported no adverse effects associated with CP (14). In recent years in the United Kingdom, CP has been preferred to morphine (5), and no serious tolerance problems have been reported. Rivers et al. did not note any complications associated with the use of high CP dosages (3–15 mg/kg per day) (21).

In our study, CP was efficacious and no adverse effects were observed in neonates with a short treatment time. A large multicentre randomized clinical trial is needed to confirm the safety and efficacy of CP. However, data on adverse effects are scarce, and thus sample size calculations would be problematic. With regards to efficacy, our study suggests that for a randomized clinical trial, the number of subjects needed to show a reduction of hospital stay from 16 to 7 days is 15 per group. Our study confirms that the randomization process should consider the type of opiates consumed by the mothers.

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