

Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants

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Objective: The purpose of this study was to test the hypothesis that treatment of neonatal opiate withdrawal (NOW) in the term infant with diluted tincture of opium (DTO) and phenobarbital was superior to treatment with DTO alone.

Study design: This was a partially randomized, controlled trial in which 20 term infants exposed to methadone and/or heroin in utero were studied. The severity of NOW was assessed by using the Finnegan scoring system. Infants were assigned to either DTO and placebo (n = 10) or DTO and phenobarbital (n = 10) when medication was required. The primary outcome variable was the duration of hospitalization. Severity of withdrawal and hospital cost were secondary outcome variables.

Results: There were no significant differences in the gestational age, growth variables, maternal methadone dose, or age at enrollment between the 2 groups. The duration of hospitalization was reduced by 48% (79-38 days) ($P < .001$) and hospital cost per patient reduced by \$35,856 ($P < .001$) for the DTO and phenobarbital group. Furthermore, these infants spent less time with severe withdrawal ($P < .04$), more time with mild withdrawal ($P < .05$), and required a lower maximum daily DTO dose ($P < .009$) when compared with the DTO-only group. The average duration of outpatient phenobarbital use was 3.5 months.

Conclusions: The combined use of DTO and phenobarbital resulted in a shorter duration of hospitalization, less severe withdrawal, and reduced hospital cost. This combination may be a preferred regimen for the treatment of NOW. (J Pediatr 2002;140:561-4)

There are currently 250,000 to 300,000 female intravenous drug abusers in the United States, 75% to 90% of whom are of childbearing age.¹ In 1996, the Na-

tional Pregnancy and Health Survey² estimated that 34,000 women used methadone during pregnancy, and an additional 36,000 pregnant women used

heroin. The number of pregnant women entering methadone programs is expected to rise, as the use and purity of heroin increases.³ Infants exposed to methadone in utero have a 60% to 80% risk of having neonatal withdrawal.⁴ This risk may approach 100% as maternal addiction escalates. Neonatal opiate withdrawal (NOW), a condition that develops as a result of the abrupt removal of the drug, is characterized by signs and symptoms of central nervous system irritability, respiratory distress, and gastrointestinal and autonomic dysfunction.⁵ The Finnegan scoring system is used to differentiate mild from severe symptoms to allow for effective treatment.⁵ Many infants remain hospitalized for weeks for treatment of withdrawal, which limits maternal bonding and increases maternal guilt.⁶ Furthermore, optimal parenting cannot occur in the neonatal intensive care setting.

There is no consensus as to the best treatment for withdrawal in the opi-

DTO Diluted tincture of opium
NOW Neonatal opiate withdrawal

ate-exposed infant. The most commonly used pharmacologic agents include opiates (diluted tincture of opium [DTO], paregoric), or barbiturates (phenobarbital).³ An opiate is preferred by some clinicians because it is more physiologic, substituting for the drug causing the withdrawal. Phenobarbital is a reasonable alternative given its sedative effects, but it does little to ameliorate some of the specific opiate-related symptoms, such as diar-

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rhea and poor feeding. We tested the hypothesis that treatment with DTO and phenobarbital is superior to DTO alone in that it lessens the severity of withdrawal symptoms, shortens the duration of hospitalization, and reduces hospital cost.

METHODS

This study was approved by the Institutional Review Boards of Women and Infants' Hospital of Rhode Island, Providence, and St Luke's Hospital, New Bedford, Massachusetts, and informed consent was obtained from the mothers.

Subject Enrollment

All term infants born at St Luke's Hospital to mothers with a history of heroin or methadone use during pregnancy were invited to enroll. One infant from each group was born at 36 to 37 weeks' gestational age but was included in the study because infants born at this gestational age are treated as term infants, and the reason for hospitalization was for withdrawal only.

Study Protocol

All aspects of care were provided to the infants in the standard fashion. Infants born at St Luke's hospital with opiate withdrawal are cared for in the level II nursery. At admission, each infant was assessed every 8 hours by the nursing staff for signs of neonatal withdrawal by using the Finnegan scoring system.⁵ If the abstinence score was >7 , the infant was randomized to either DTO (McKesson, Methuen, Mass) and placebo or DTO and phenobarbital and started on medication. The criteria for starting medication was based on the recommendation of Finnegan et al.⁵ The nurses who assigned the Finnegan score and who administered medications were masked to group assignment, as the study drug (phenobarbital or placebo) was similar in appearance. This was a partially randomized, con-

trolled trial in which infants were prospectively matched for severity of withdrawal as measured by the first Finnegan score >7 . Specifically, every subject from the DTO and placebo group had a counterpart from the DTO and phenobarbital group with the same Finnegan score ± 1 . If the infant had no match, he was randomly assigned to a group. The pharmacist and laboratory technician were notified of patient grouping at the time of enrollment. Because it is nursery policy to obtain a weekly hematocrit on all long-term patients, infants from the DTO and phenobarbital groups had extra blood drawn to measure the phenobarbital level. Blood sampling occurred behind a screen for study patients. Phenobarbital levels were reported to the physician only, through the hospital e-mail system. Values were not available in the written or computerized chart until discharge, when the laboratory technician entered the phenobarbital levels into the record.

The starting dose of DTO (0.4 mg/mL morphine) was 0.05 mL/kg 6 to 8 times per day given with feedings. This dose was increased in 0.1 mL increments if the withdrawal score remained >7 , was maintained if the score ranged from 5 to 7 inclusive, and was reduced by 0.1 mL decrements if the score was <5 for 3 consecutive 8-hour shifts. The study drug was administered with the first DTO dose by giving the patient a loading dose of 30 mg/kg of study drug (3 oral 10 mg/kg doses 12 hours apart to avoid emesis), followed by maintenance therapy (5 mg/kg/day divided twice daily) starting 12 hours after the last loading dose to achieve a level of 20 to 30 mg/dL. This phenobarbital level controls 94% of withdrawing patients adequately.⁷ The phenobarbital dose was adjusted on the basis of the weekly level, whereas the placebo dose was adjusted in a similar fashion to maintain masking. Once the DTO was discontinued, the infant remained hospitalized for an additional 48 hours to assess for residual withdrawal, after

which the code was broken, and if the infant was given phenobarbital, he was sent home on phenobarbital to be weaned by his private practitioner. The use of outpatient phenobarbital for residual NOW is common practice at St Luke's, and specific recommendations with respect to outpatient management were not modified for this study.

The maternal toxic screen and methadone dose at the time of delivery were recorded. Maternal substance use history throughout pregnancy was obtained from the record and patient reporting. Neonatal characteristics including age at enrollment, birth and discharge morphometric data, and gestational age were collected. Maximum DTO dose, duration of hospitalization, duration of DTO use, and Finnegan scores during hospitalization were documented. Total hospital charges for each patient, exclusive of physician billing, were obtained from the hospital billing department.

Calculations and Statistical Analysis

To demonstrate a 30% reduction in hospital days by using a power of 0.80 and an α of .05 for a 2-tailed test, 24 infants were required in each group for a total of 48 patients. Approximately midway through the enrollment period, the data were analyzed by an individual not directly involved with the study, and the decision was made to stop enrolling patients because significance was reached with a smaller sample size. Data are presented as mean \pm SD. Two-tailed Student *t* tests were used to determine differences between the groups, and when appropriate, the Pearson correlation coefficient was used. The Mann-Whitney *U* test was used to compare median values between groups.

RESULTS

Twenty-three infants met entry criteria (history of maternal heroin or methadone use during pregnancy) be-

tween March 1998 and May 2000. Two of these infants did not require medication for opiate withdrawal. The remaining 21 mothers gave consent, but one infant was excluded from the study because of transfer to a tertiary care facility when congenital heart disease was diagnosed. The remaining 20 infants were randomized to receive either DTO and placebo (n = 10) or DTO and phenobarbital (n = 10).

There were no significant differences in the gestational age (39.7 ± 1 weeks vs 39.1 ± 2 weeks), birth weight (2897 g ± 474 g vs 3111 g ± 416 g) head circumference (32.9 cm ± 2.2 cm vs 33.4 cm ± 1.5 cm) or length (49.7 cm ± 2.4 cm vs 49.6 cm ± 3.3 cm) between the placebo and phenobarbital groups. Growth percentiles at discharge were similar between groups whether the mean or median values were compared. Because the range of growth percentiles is not evenly distributed, the median values are presented. The discharge percentiles for the DTO-only group were 25%, 25%, 38% for weight, head circumference, and length, respectively, versus 25%, 38%, and 62% for infants from the DTO and phenobarbital group. Eighty percent of infants from both groups were begun on medications by day of life 1 and 20% by day of life 2. There were no other medical problems that affected the duration of hospitalization. All infants in the study were exposed to methadone, with the exception of one subject from the DTO and placebo group who was exposed to heroin only. The mean maternal methadone dose did not differ statistically between groups (105 mg ± 52 mg vs 71 mg ± 30 mg). Because the doses were not evenly distributed, the median values were also compared (98 mg for the DTO and placebo group and 67.5 mg for the DTO and phenobarbital group), and differences were not statistically significant. The range of maternal methadone doses was 30 mg to 180 mg for the DTO and placebo group and 25 mg to 120 mg for the DTO and phenobarbital group. The correlation between mater-

Table. Severity of withdrawal

	DTO + placebo (n = 10) (% ± SD)	DTO + Phenobarbital (n = 10) (% ± SD)	P value
Finnegan score during hospitalization			
≥8	15 ± 6	10 ± 5	.04
≥5 and ≤7	32 ± 5	26 ± 8	.08
≤4	53 ± 9	64 ± 10	.03
Maximum daily DTO dose (mL)*	16.8 ± 12	4.7 ± 2.7	.009

*M ± SD.

nal methadone dose and duration of hospitalization was not statistically significant ($P > .05$). The use of other illicit substances during pregnancy did not differ between groups.

The average duration of hospitalization was 79 days for patients receiving DTO alone (range, 51-118 days) compared with 38 days for infants receiving DTO plus phenobarbital (range, 15-70 days) ($P < .001$). This reduction was significant even when controlling for maternal methadone dose ($P < .004$). The median values for the duration of hospitalization were also significantly different (77 days vs 32 days) ($P < .001$). The duration of DTO use was 76 days ± 22 days for infants receiving DTO alone and 35 days ± 21 days for infants receiving DTO and phenobarbital ($P < .001$). Similarly, this too was significant when controlling for maternal methadone dose ($P < .005$).

The average hospital cost for an infant receiving DTO alone was \$69,200 ± \$19,671 (range, \$45,316-\$103,829) versus \$33,344 ± \$17,935 (range, \$20,360-\$63,556) for an infant receiving DTO and phenobarbital ($P < .001$), representing an average cost savings of \$35,856 per patient in the latter group. Hospital cost was positively correlated with maximum neonatal DTO dose ($r = 0.81$, $P < .001$), but not with maternal methadone dose. The average phenobarbital level was 29 mg/dL (range, 7-46 mg/dL).

Two measures were employed to determine the severity of withdrawal. By

using the Finnegan score, a comparison was made between the two groups (Table). The infants receiving DTO alone spent a significantly greater period with a score >7 ($P < .04$), and the infants receiving DTO and phenobarbital spent a significantly greater period of time with scores <5 ($P < .03$). The second measure of withdrawal severity was the maximum daily dose of DTO required to treat symptomatic withdrawal. The infants who received DTO only required a maximum daily DTO dose of 16.8 mL ± 3.7 mL versus 4.7 mL ± 2.7 mL for the infants receiving DTO and phenobarbital ($P < .009$).

No infant in the study had seizures or was rehospitalized at St Luke's Hospital for symptoms of withdrawal. Although the decision to maintain infants on phenobarbital as an outpatient was left to the private pediatrician and not the investigators, the average duration of use once the infant was sent home was 3.5 months (range, 2-9 months).

DISCUSSION

The 2 common agents used to treat neonatal withdrawal are opiates and phenobarbital.³ Carin et al⁸ found no difference in the efficacy of DTO versus phenobarbital, yet opiates were determined to be superior to phenobarbital by Kandall et al⁹ because of a lower incidence of seizures, and by Kron et al¹⁰ because of improved sucking, higher

caloric intake, and better weight gain in the opiate-treated infants. There is evidence that opiate-treated infants require a longer period of pharmacologic intervention.⁸ In opiate-addicted experimental animals, conversion of tyrosine to norepinephrine and dopamine in the central nervous system depends on the administration of progressively larger doses of morphine.¹¹ During withdrawal, the brain regains its ability to synthesize catecholamines. Neonatal abstinence syndrome may be associated in part with abnormal metabolism of these mediators, and continued use of opiates may inhibit the restoration of their normal synthesis.¹¹ The alternative medication, phenobarbital, enhances microsomal enzymatic function which facilitates the disposition and excretion of the opiate to which the infant is transplacentally addicted.⁹ This may promote the depletion of opiate stores and render the infant more prone to severe withdrawal. As such, phenobarbital and DTO together might be the optimal treatment because phenobarbital would enhance the depletion of opiate stores, whereas small amounts of DTO would avoid the acute severe symptoms, such as seizures that might develop in the absence of additional opiate.

The phenobarbital dose used for this study is similar to doses reported previously.⁷ Infants who received DTO and phenobarbital had no compromise in growth, nor were they heavily sedated. Because the private practitioners in the area are familiar with the outpatient use of phenobarbital for residual withdrawal, the investigators did not attempt to create a stringent outpatient weaning schedule. The pediatricians rely on parental input, physical examination, and phenobarbital levels when making decisions about weaning. When the infant was comfortable, most pediatricians let the baby outgrow the dose.

We demonstrated the extent of neonatal withdrawal from maternal methadone doses >100 mg. Current literature does not account for contem-

porary maternal methadone requirements.^{12,13} Counseling parents about newborn withdrawal on the basis of current literature may not be appropriate when dealing with a population such as the subjects of this report.

The published incidence of neonatal withdrawal requiring pharmacotherapy ranges from 60% to 80%. In our hospital population, 91% of the infants born to an opiate-addicted mother required therapy and are the subjects of this report. The likely reason for this increased incidence of significant withdrawal is because of the degree of heroin addiction in pregnant women, resulting in an increased methadone requirement.

The current report is a small study and does not address the long-term outcome for these infants. Because the preterm infant experiences less severe withdrawal when compared with the term infant,¹⁴ only term infants were the subjects of this report. Therefore, recommendations for the preterm infant cannot be made based on our findings.

In summary, the use of DTO and phenobarbital for the treatment of NOW compared with DTO alone lessens the severity of withdrawal, shortens hospitalization, and reduces hospital cost. DTO and phenobarbital may be the preferred treatment for NOW. With these findings, it is hoped that a larger clinical trial will occur to definitively address not only the optimal medical management for this population but also the long-term follow-up for these exposed infants.

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