

A Clinical Trial Assessing the Efficacy and Safety of a New Injectable Formula of Sodium Phenobarbital Containing No Additives for the Treatment of Neonatal Seizures

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Aims : A new phenobarbital preparation for injection containing no additives (NOBELBAR[®]) was developed in Japan for safer use in neonates with seizures. This study was conducted to evaluate the clinical efficacy and safety of NOBELBAR[®] for the treatment of neonatal seizures.

Methods : This investigator-initiated clinical trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice. Phenobarbital was initially administered intravenously at a loading dose of 20 mg/kg. An additional dose of 20 mg/kg was given if the seizures did not resolve. The primary efficacy was evaluated 30 minutes after the administration of the loading dose. Infants who responded to the loading administration received maintenance therapy with 2.5 to 5 mg/kg intravenous phenobarbital once daily for 6 days.

Results : NOBELBAR[®] was administered to 10 neonates with seizures. The primary efficacy was evaluated as complete response in all patients. Adverse events were reported in 9 of the 10 patients (90%), most of which were mild. Plasma phenobarbital concentrations ranged from 18.7 to 45.3 $\mu\text{g/mL}$.

Conclusion : The study demonstrated that NOBELBAR[®] was effective for the control of neonatal seizures, and plasma drug concentrations were maintained within the therapeutic range. Approved for manufacturing and marketing was obtained based on the results of this study and other relevant data.
(Clinical Trials, number, UMIN-C000000410, JMA-II A00002.)

Key words : phenobarbital, neonatal seizures, good clinical practice, investigator-initiated clinical trial

Introduction

A lyophilized product of phenobarbital sodium entirely free of additives was used in this study.

In Japan, no phenobarbital preparation for intravenous injection was available despite an increasing demand for such product in neonatal care. An

intravenous phenobarbital was discontinued in the 1980's, and Japanese neonatologists had no choice but to give intramuscular phenobarbital preparation intravenously or use imported intravenous phenobarbital products. Furthermore, due to the instability of phenobarbital sodium in water, the available phenobarbital injection preparations contain organic sol-

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vents such as benzyl alcohol¹⁾ and propylene glycol²⁻⁴⁾, which are often hazardous to premature and neonatal infants. Therefore, there is a strong demand for the development of a phenobarbital preparation for intravenous injection that is free of these additives.

The Japan Pediatric Society (JPS) has been appealing to the Ministry of Health, Labour and Welfare (MHLW) for the medical need of appropriate phenobarbital preparations for neonatal seizures. The JPS finally succeeded in negotiating with Norbelpharma Co., Ltd. develop a new additive-free phenobarbital intravenous solution. Nobelpharma Co., Ltd. offered to supply an investigational drug in response to the appeal. This clinical trial, which was an investigator-initiated clinical trial⁵⁻⁷⁾, was funded by the MHLW and organized by physicians with the aim to obtain regulatory approval of the new phenobarbital preparation.

Methods

Study Design and Patients

This clinical trial was supported by the clinical trial promotion program subsidized by the Japan Medical Association with the Ministry of Health, Labour and Welfare Research Grant. The grant numbers were CCT-A-1601, CCT-B-1605, CCT-C-1661-8. This trial was an open-label, uncontrolled, multicenter study, conducted in compliance with the good clinical practice (GCP). Eight hospitals were enrolled in this trial. The protocol of this study was reviewed and approved by the institutional review board of each study site as well as the relevant regulatory agency. The quality of the trial was controlled by monitoring, data management and an independent assessment committee.

This study was conducted from March 2006 to March 2007, and registered with clinical trials numbers of UMIN-C000000410 and JMA-II A00002.

A diagnosis of neonatal seizure was made by two or more pediatricians using the following criteria⁸⁾: a) at least two episodes of unprovoked movement sequences; b) such movement sequences contained no paroxysms of ankle clonus or premature infant apnea; c) seizures consisted of spontaneous, tonic, myoclonic, focal or multifocal limb movements, or facial and eyelid twitching, sucking, and chewing movements; and d) all these movements being frequent and stereotyped.

To ensure the parents' understanding of the trial in

making decisions for enrollment of their child who was acutely experiencing seizures, parents of the candidate infants were explained about the trial beforehand. The criteria for inclusion as candidates were as follows: a) abnormal movements suggestive of neonatal seizures; b) neonatal asphyxia with an Apgar score below 5 at 5 minutes post partum and a base deficit of 10 mmol/L or greater on admission; c) birth trauma; d) infection or anomaly of the central nervous system; and e) hypoglycemia or electrolyte abnormality with abnormal movements suggestive of neonatal seizures.

The candidate infants were further assessed for neonatal seizure. Neonatal seizure was defined as either one of the following: a) acute neonatal seizures in addition to any of the criteria a) to d) for candidate infants (listed above), or b) persistent abnormal movements indicative of neonatal seizures despite correction of hypoglycemia and electrolyte abnormalities in infants fulfilling the criterion e) for candidate infants.

Once the infants met the eligibility criteria for neonatal seizure, they were enrolled in the trial after written informed consent was obtained from the parents.

In the case that the parents were able to receive full explanation of the trial before treatment started, infants whose parents did not receive prior explanation could also be enrolled in the trial after written informed consent was obtained.

Procedures

The treatment consisted of loading administration and maintenance therapy. In the loading administration, the study drug was injected intravenously at a dose equivalent to 20 mg/kg of phenobarbital over 5 to 10 minutes. If neonatal seizures failed to resolve within 30 minutes after initiation of the dose, an additional 20 mg/kg dose was administered over 5 to 10 minutes. Responders (i.e., patients with an excellent or good response) to the loading administration received maintenance therapy with 2.5 to 5 mg/kg phenobarbital intravenously once daily, which was initiated approximately 24 hours after the loading administration or after the last loading dose in the case that any additional dose was given. If recurrence of seizures was observed before initiation of maintenance therapy, an additional dose of 5 to 20 mg/kg intravenous infusion over 5 to 10 minutes was allowed

Table Demographic characteristics of subjects and results of the primary efficacy evaluation

Case No.	Gender	Birth weight (g)	Gestational age	Age in days	Birth place	Cause of seizure*	Seizure type	Investigator's evaluation	IAC's evaluation
1	F	2,274	37w 6d	1	Out-of-hospital	Fetal distress*	Subtle	Excellent	Excellent
2	M	3,650	40w 2d	3	Out-of-hospital	Fetal distress*	Tonic, Clonic	Excellent	Excellent
3	M	2,880	39w 2d	2	Out-of-hospital	Unknown	Clonic	Excellent	Excellent
4	M	2,121	34w 5d	1	Out-of-hospital	Hypoxic ischemic encephalopathy	Myoclonic	Excellent	Excellent
5	M	1,144	33w 1d	4	Out-of-hospital	5p ⁻ syndrome	Subtle	Excellent	NA
6	M	3,122	38w 1d	4	In-hospital	Hypocalcemia	Clonic	Excellent	Excellent
7	M	3,178	41w 1d	2	Out-of-hospital	Hypoxic ischemic encephalopathy	Subtle	Excellent	Excellent
8	M	3,530	39w 6d	2	Out-of-hospital	Unknown	Clonic, Subtle	Excellent	NA
9	F	2,982	38w 3d	1	Out-of-hospital	Neonatal cerebral infarction	Tonic, Clonic, Subtle	Good**	Good
10	M	3,796	39w 3d	5	In-hospital	Subarachnoid hemorrhage	Tonic, Subtle	Excellent	Excellent

* : Including suspected causes

** : Changed to excellent after additional dosing

IAC : Independent assessment committee

M : Male

F : Female

NA : not applicable

as long as the patient's plasma drug concentration was confirmed to be below 40 $\mu\text{g/mL}$.

Outcome Measures

The primary efficacy endpoint was clinical response evaluated 30 minutes after initiation of the dose, and was rated as excellent (seizures resolved), good (seizures reduced in severity or frequency to about half), or poor (seizures reduced in severity or frequency to less than about half). The evaluation was performed by two or more pediatricians. A secondary assessment of the diagnosis of neonatal seizures and clinical efficacy was conducted by an independent assessment committee composed of three members including pediatricians/pediatric neurologists, based on the video of each patient recorded for 30 minutes preceding the initial administration. For each patient, the frequency and type of neonatal seizures reported during the study were assessed at the completion of

maintenance therapy. Furthermore, data for adverse events, vital signs, and laboratory tests including hematology and blood biochemistry were collected throughout the follow-up period of one week after the last dosing.

The plasma concentration of phenobarbital was determined 2 hours after initiation of the loading or additional dose at the same time as the evaluation of the primary endpoint, 2 hours after the first maintenance dose, and prior to the final dose of maintenance therapy, or at the time of discontinuation in the case of withdrawal from the study. The relationship between plasma drug concentration and efficacy was analyzed.

Results

The demographic characteristics of the subjects and results of efficacy evaluation are shown in Table.

A total of 10 subjects were enrolled in this clinical trial, with a mean postnatal age of 2.5 days (range : 1

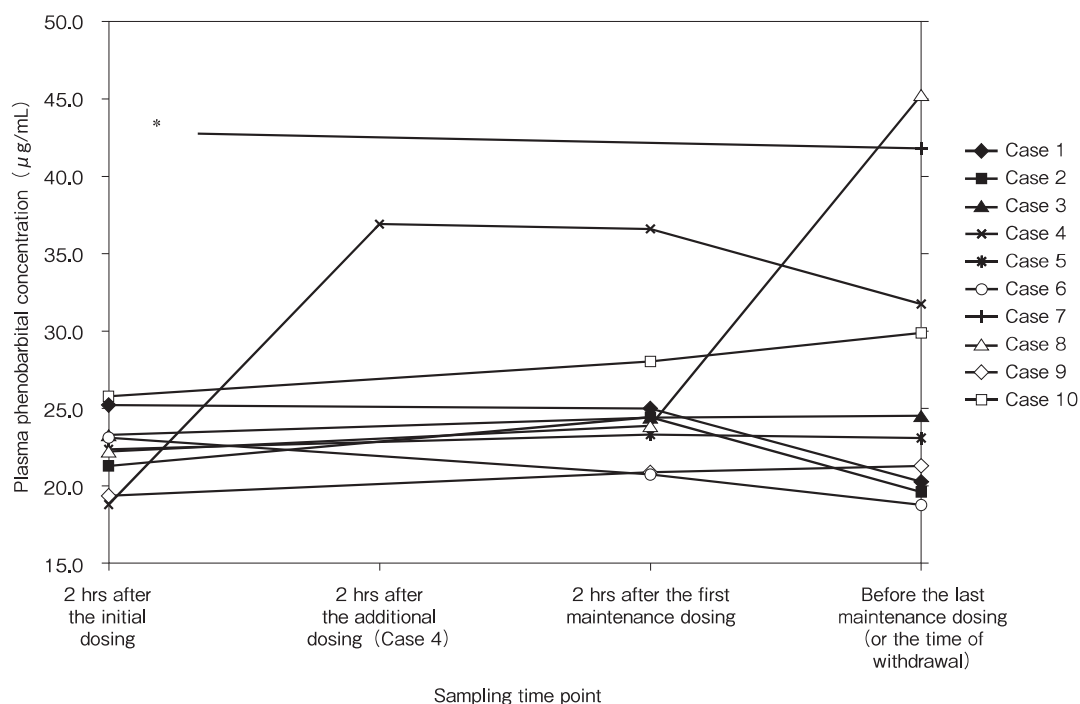


Fig. Plasma concentrations of phenobarbital over time in 10 patients

Plasma phenobarbital concentrations ranged from 20 to 25 $\mu\text{g/mL}$ after the initial loading administration and were approximately 40 $\mu\text{g/mL}$ following additional dosing.

The plasma drug concentrations were maintained at 18 to 32 $\mu\text{g/mL}$ during maintenance therapy in all but one patient.

*2 hrs after the additional dosing (Case 7)

to 5 days), mean birth weight of 2,867 g (range : 1,144 to 3,796 g), and mean gestational age of 38.2 weeks (range : 33.1 to 41.1 weeks). All subjects were confirmed to have neonatal seizures by the independent assessment committee. The results of diagnosis of neonatal seizures provided by the independent assessment committee were consistent with those obtained by the investigators.

Seizures were resolved after administering the 20 mg/kg loading dose in 9 of the 10 patients, and after an additional loading dose (20 mg/kg) in the remaining 1 patient. Therefore, the clinical response evaluated 30 minutes after the loading administration including any additional dosing was rated as excellent in all patients by the investigators on site. Evaluation by the independent assessment committee yielded an excellent response at 30 minutes after the initial administration in 7 patients and good response in 1 patient. The response was not assessable in the remaining 2 patients due to blurred images of the videos. Maintenance therapy was given to all patients, except one (Case 7) who had received pentobarbital, which violated the protocol. One patient (Case 4)

received an additional phenobarbital dose of 20 mg/kg for recurrence of seizures before entering the maintenance phase. Eight of 9 patients who started maintenance therapy completed the maintenance therapy. One (Case 9) of nine patients who had received pentobarbital, which violated the protocol. Seizure recurrence was noted in 1 patient during the period of maintenance therapy, and this patient received an additional 20 mg/kg dose.

Plasma phenobarbital concentrations over time for each patient are shown in Figure. The plasma concentrations of the drug were within the range of 20 to 25 $\mu\text{g/mL}$ in all patients with the exception of 2 patients (Cases 4 and 7) who received an additional phenobarbital dose. The plasma phenobarbital concentrations in the 2 patients receiving an additional loading dose were nearly twice as high as those observed after the initial dosing. One patient (Case 8) had a plasma phenobarbital concentration of 45.3 $\mu\text{g/mL}$ before the final maintenance dosing. The plasma drug concentrations were 22.2 $\mu\text{g/mL}$ two hours after the initial dosing and 23.9 $\mu\text{g/mL}$ two hours after the first maintenance dosing. This patient

received an initial loading dose of phenobarbital at 19.8 mg/kg and then maintenance therapy at 5.0 mg/kg/day for 3 days, reducing to 2.5 mg/kg/day thereafter. Excluding this patient, only the patients given an additional loading dose had plasma drug concentrations exceeding 30 $\mu\text{g/mL}$ during the maintenance treatment.

During the study, adverse events were reported in 9 of the 10 patients. Adverse events included respiratory depression in 4 patients (Cases 1, 2, 8 and 9), and bradycardia (Cases 8 and 9), eczema (Cases 1 and 8) and decreased oxygen saturation (Cases 2 and 3) in 2 patients each. Adverse drug reactions were reported in 6 of the 10 patients, including respiratory depression (Cases 1, 2 and 9) in 3 patients, decreased oxygen saturation (Cases 2 and 3) in 2 patients, and bradycardia (Case 9), increased bronchial secretion (Case 7), hypotension (Case 4) and decreased urine volume (Case 3) in 1 patient each.

Most adverse events were mild, except one case each of moderate respiratory depression (Case 2), moderate renal failure (Case 5) and severe patent ductus arteriosus (Case 5). Of these adverse events, only respiratory depression was considered to be related to the study drug. No adverse event was related to high plasma drug concentrations.

The changes in vital signs from baseline were calculated at each assessment point, and there was a decrease in systolic blood pressure 1 hour after the initial loading dose (mean $\pm$ SD, -8.8 ± 10.1 mmHg ; $p < 0.1$). Systolic blood pressure (mean $\pm$ SD) before the initial loading dose was 70.1 ± 14.9 mmHg.

No hematological or blood biochemical abnormalities attributable to the administration of the study drug were noted in the present series.

Discussion

This study was performed to evaluate the new injectable phenobarbital preparation containing no additives for the treatment of neonatal seizures.

Since this was an open-label, uncontrolled study, an independent assessment committee was organized to ensure standardized application of the evaluation criteria among study sites. The committee independently assessed the diagnosis of neonatal seizures and the efficacy of the study drug, and the results were compared with those evaluated by each investigator. The primary efficacy evaluation performed by the investigators was found to be consistent with those by

the independent assessment committee, corroborating the efficacy of the study drug.

After the loading dose of 20 mg/kg, plasma phenobarbital concentration rapidly reached the therapeutic range of 20 to 25 $\mu\text{g/mL}$. These levels were consistent with previous reported data^{9,10}. The maintenance phenobarbital therapy at 2.5 to 5 mg/kg/day also resulted in stable and sustained therapeutic plasma drug concentrations. One patient (Case 8) had a high plasma drug concentration of 45.3 $\mu\text{g/mL}$ prior to the final dose of maintenance therapy, which was very different from those observed in the remaining patients. It remains unknown why the plasma drug level increased before the final dose of maintenance therapy in this patient, but a low clearance and a protracted elimination half-life of phenobarbital in newborns at the early postnatal stage¹¹ could explain the elevation, particularly since the maintenance therapy was started at a relatively high dose in this patient. A previous study has shown that maintenance therapy with phenobarbital at 5 mg/kg/day may result in an increased plasma drug level of approximately 40 $\mu\text{g/mL}$ ¹².

Adverse drug reactions such as respiratory depression and decreased oxygen saturation were observed in 6 of the 10 patients. Most of these reactions were mild. The adverse reactions observed in this study have already been shown to be associated with the use of phenobarbital. Decreased systolic blood pressure was noted 1 hour after the initial loading dose. The cause of decreased blood pressure was obscure, because it was difficult to distinguish between resolution of convulsion and direct drug action. These findings suggest a need to monitor the neonates' condition carefully for any respiratory depression or decreased blood pressure after intravenous phenobarbital administration.

The adverse event profile observed in the patient with high plasma drug concentration did not differ from those seen in other patients; the elevated plasma drug concentration appeared to have no influence on the adverse event profile within the range of plasma drug concentrations observed in this study (18.7 to 45.3 $\mu\text{g/mL}$).

The above results thus indicate that the new phenobarbital preparation for injection (NOBELBAR[®]) is effective for the treatment of neonatal seizures at the dosage examined in the present trial. In addition, there is no particular safety concern except predicta-

ble adverse reactions related to the known pharmacological effects of the drug.

The phenobarbital preparation was approved for manufacturing and marketing based on the results of this study and other relevant data. The product has been marketed for the treatment of neonatal seizures and status epilepticus since December 2008 in Japan under the brand name NOBELBAR® 250 mg for injection. Post-marketing surveillance is currently ongoing to further confirm the safety of this solution.

This is the first investigator-initiated GCP-compliant clinical trial performed in the NICU emergency setting in this country. Although the number of patients was small, the study was conducted using the same standard as industry-sponsored clinical trials. There were two major protocol violations (use of pentobarbital). Apart from that, there were only minor protocol violations. Using the data, the drug was approved in Japan. We hope that other new preparations will be approved with based on investigator-initiated clinical trials in Japan.

Conflict of Interest

There is no conflict of interest in conduct of the present clinical trial and release of the results.

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