

Original Article

Efficacy of direct hemoperfusion for the removal of phenobarbital through blood concentration analysis

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Aim: Phenobarbital overdose can cause coma and even death. The consciousness disturbance is often prolonged due to its long half-life. In this study, we investigated the efficacy of direct hemoperfusion (DHP) for the removal of phenobarbital by measuring the blood levels of phenobarbital.

Methods: Study subjects included five patients with phenobarbital poisoning who were transferred to our hospital. Direct hemoperfusion was carried out in three of the five patients (six times in total), and the elimination rate was calculated by measuring the blood levels before and after DHP. Furthermore, the disappearance rate of phenobarbital without DHP was calculated in all five patients (seven times in total) for comparison with the elimination rate.

Results: The elimination rate of phenobarbital with DHP was significantly higher than the disappearance rate without DHP.

Conclusion: This study suggests that early introduction of DHP should be considered as a treatment option for phenobarbital poisoning.

Key words: Activated charcoal, direct hemoperfusion, phenobarbital poisoning, plasma phenobarbital level, prolonged coma

INTRODUCTION

PHENOBARBITAL IS A long-acting barbiturate with hypnotic properties. Phenobarbital overdose can cause coma, shock, dyspnea, and even death.¹ Although it is metabolized by the liver and excreted in the urine, it has a long half-life (53–118 h).² Phenobarbital has a molecular weight of 232, a distribution volume of 0.7 L/kg, and a protein-binding rate of 50%. Hemodialysis (HD) and direct hemoperfusion (DHP) have been reported to be effective for the removal of phenobarbital. In this study, we investigated the efficacy of DHP for the removal of phenobarbital by comparing the changes in blood levels before and after DHP with the changes during conservative treatment in five patients with phenobarbital poisoning.

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METHODS

STUDY SUBJECTS INCLUDED five patients with phenobarbital poisoning who were transferred to our hospital between December 2007 and March 2018. The five patients were retrospectively reviewed using the medical records. In many cases, it was unclear whether the patient had taken an overdose of other drugs at the same time, so we did not describe in detail.

On admission, all patients underwent gastric lavage and received activated charcoal treatment. Activated charcoal was given once to all patients except for one case with prolonged consciousness disturbance. Four patients had prominent consciousness disturbance (Glasgow Coma Scale score 3). Direct hemoperfusion was undertaken in three of the four patients. One of the cases with Glasgow Coma Scale score 3 on admission (case 2) was treated conservatively with tracheal intubation as the main cause of the coma was presumed to be benzodiazepines and his respiratory status was stable. The patient's state of consciousness gradually improved thereafter, so DHP was not carried out. The procedural time of a single DHP treatment was 3 h. The hemoperfusion adsorption column Hemosorba CHS (Asahi Kasei

Medical, Tokyo, Japan) was used for DHP. Unfractionated heparin was used as the anticoagulant. Direct hemoperfusion was undertaken on consecutive days until the patient became awake and alert, and it was completed after the recovery of consciousness.

The blood levels of phenobarbital were measured following routine clinical practice as follows: at the time of admission and at the time of daily blood tests in the morning (in case of prolonged consciousness disturbance during hospitalization). Additional measurements were carried out as needed when DHP was considered. The mean phenobarbital elimination rate per hour (%/h) was calculated from blood levels measured before and after DHP, and the mean disappearance rate per hour without DHP was calculated from blood levels measured in routine blood testing and used for comparison.

The phenobarbital elimination rate with DHP and the phenobarbital disappearance rate without DHP were calculated using the following formula:

The elimination rate or disappearance rate (%/h) = (pre-treatment blood level – post-treatment blood level) / pre-treatment blood level × 100/h.

Statistical analyses of the changes in blood levels and the comparison between removal rate and disappearance rate were carried out using the Wilcoxon signed-rank test. The significance level was set at $P < 0.05$.

RESULTS

TABLE 1 shows the background characteristics of the five patients, including sex, phenobarbital dose, consciousness level, blood test results (aspartate aminotransferase, alanine aminotransferase, total bilirubin, γ -glutamyl transpeptidase, blood urea nitrogen, and creatinine) on admission, number of days to awakening, number of DHP sessions, and outcome. The mean age of the patients was 37.4 years, and all were women. The blood test results on admission showed no renal or liver dysfunction in any patient. The elimination rate was calculated from blood levels measured before and after DHP in three patients (six times in total). The disappearance rate without DHP was calculated in all five patients (seven times in total). Figure 1 depicts the changes in blood levels for each patient. The blood levels showed a significant difference after DHP. There were almost no changes in blood levels under the condition without DHP, although a statistical analysis of the change was not carried out because of variation in the test intervals. Figure 2 shows the results of comparison between the elimination rate and the disappearance rate per hour. The phenobarbital disappearance rate without DHP was found to be extremely low. The phenobarbital

Table 1. Background of five patients with phenobarbital overdose

Patient	Age (years)	Sex	Dose of phenobarbital (drug name)	Consciousness level on admission	AST (IU/L)	ALT (IU/L)	T-Bil (IU/L)	γ -GTP (IU/L)	BUN (mg/dL)	Cre (mg/dL)	Mechanical ventilation	Number of DHP sessions (times)	Time to awakening (h)	Outcome
1	23	Female	450 mg (Vegetamin A)	GCS 11 (E2V4M5)	14	7	0.1	12	6.0	0.71	–	0	11	Survived
2	23	Female	Unknown (Phenobar)	GCS 3 (E1V1M1)	13	9	0.1	19	4.5	0.64	–	0	12	Survived
3	41	Female	7,020 mg (Vegetamin B)	GCS 3 (E1V1M1)	37	21	0.2	24	18.2	0.99	+	2 (day 1, 2)	16	Survived
4	43	Female	Unknown (Phenobar)	GCS 3 (E1V1M1)	17	25	0.5	44	7.5	0.65	+	2 (day 2, 3)	40	Survived
5	57	Female	3,450 mg (Phenobar)	GCS 3 (E1V1M1)	17	58	0.6	31	11.8	0.64	+	2 (day 3, 4)	102	Survived

γ -GTP, γ -glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; GCS, Glasgow Coma Scale; T-Bil, total bilirubin.

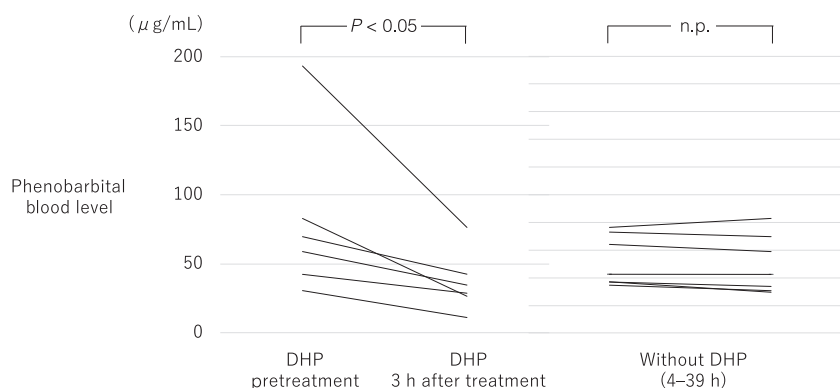


Fig 1. Changes in phenobarbital blood levels in overdose patients treated with or without direct hemoperfusion (DHP).

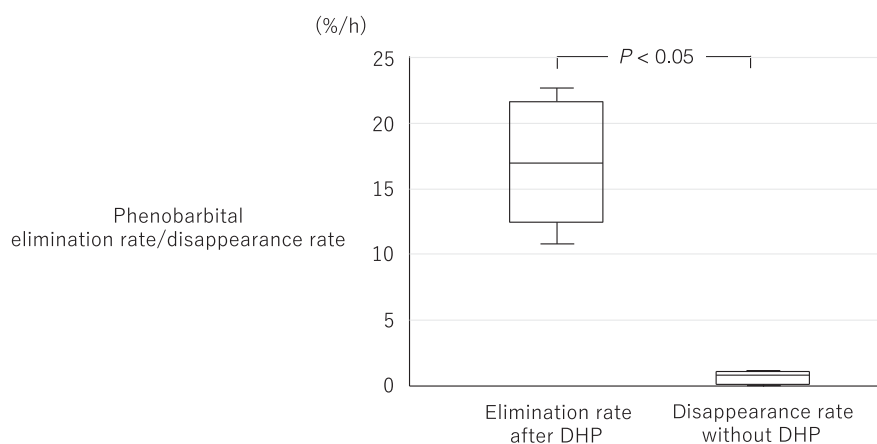


Fig 2. Comparison of elimination rate ($n = 7$) and disappearance rate ($n = 7$) of phenobarbital per hour between patients treated with or without direct hemoperfusion (DHP).

elimination rate with DHP was found to be significantly higher than the disappearance rate without DHP. Of the seven measurements of the disappearance rate without DHP, four were obtained immediately after treatment with activated charcoal (Table 2), but it was not considered to significantly affect the result.

DISCUSSION

PHENOBARBITAL POISONING IS a fatal condition as it can cause prolonged consciousness disturbance due to its long half-life.³ Therefore, rapid and appropriate treatment is important, especially in patients with severe conditions.

In a systematic review by Roberts *et al.*, 94 cases of barbiturate poisoning were extracted from reports published before 2011, and there were 52 cases in which barbiturate clearance and treatment efficiency were calculated.⁴ Based on the analysis, they concluded that urinary alkalization

was ineffective, but multiple-dose activated charcoal treatment was effective. In 2014, the Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup developed recommendations for the extracorporeal treatment of barbiturate poisoning.⁵ According to the recommendations, blood purification therapy is indicated when any of the following conditions are met: (i) prolonged coma is present or expected, (ii) presence of shock after fluid resuscitation, (iii) persistence of toxicity despite multiple-dose activated charcoal treatment, (iv) increase in serum barbiturate concentration despite multiple-dose activated charcoal treatment, (v) presence of respiratory depression necessitating mechanical ventilation. Regarding treatment methods, HD is recommended as the first-line option for blood purification therapy and, if it is unavailable, DHP or continuous renal replacement therapy is recommended.

According to the recommendations, patients with phenobarbital poisoning should first receive multiple-dose

Table 2. Changes in phenobarbital blood levels in overdose patients treated with or without direct hemoperfusion (DHP)

Patient no.		Pretreatment blood level ($\mu\text{g/mL}$)	Elapsed time (h)	Post-treatment blood level ($\mu\text{g/mL}$)	Elimination rate (%/h)
1	After admission (after activated charcoal treatment)	36.9	4	29.4	5.9
2	After admission (after activated charcoal treatment)	36.8	9	33.6	1.0
3	Between initial DHP and second DHP	76.3	6	82.8	-1.4
4	After admission (after activated charcoal treatment)	72.9	4	69.6	1.1
4	Between initial DHP and second DHP	42.4	7	42.3	0.0
5	After admission (after activated charcoal treatment)	64.0	39	58.8	0.2
5	Between initial DHP and second DHP	34.5	14	30.5	0.8
Mean \pm SD		52.0 \pm 18.4	11.9 \pm 12.5	49.6 \pm 21.1	1.0 \pm 2.0

activated charcoal treatment to improve the consciousness level. However, the results of the present study showed that single treatment with activated charcoal is not expected to be effective, and multiple-dose treatment could take some days to lower the blood level. There are case reports supporting this notion.⁶ Therefore, it is likely that multiple-dose activated charcoal treatment could take a long time to be effective and result in prolonged consciousness disturbance. We believe that it would be unnecessary to wait for the effect of multiple-dose activated charcoal treatment and increase the risk in patients with coma. Therefore, we believe that aggressive blood purification should be carried out to improve the level of consciousness as early as possible.

In addition, according to the recommendations by the EXTRIP Workgroup, HD is preferred over DHP based on the considerations reported by Shannon.⁷ Shannon compared the efficacy of HD and DHP for severe theophylline toxicity and reported that DHP was comparable to HD in terms of clearance ability. One of the reasons for preferring HD was that DHP is associated with extremely high risks of complications, including thrombocytopenia, hypocalcemia, and bleeding due to increased heparin. The other reasons for preferring HD were its lower cost, less experience with DHP, and unavailability of DHP cartridges in some countries. In the present study, DHP was undertaken in all patients, but there were no remarkable adverse reactions, including the abovementioned complications. In Japan, both HD and DHP are covered by health insurance, and DHP is available in institutions where blood purification therapy is available in daily clinical practice; thus, there are no technical difficulties in carrying out DHP. Therefore, in Japan, there may be no reasons to strongly prefer HD over DHP. In addition, in some institutions, HD is carried out only in the blood purification room. In contrast, DHP does not require

dialysis fluid and can be undertaken outside the blood purification room using a bed console alone. Direct hemoperfusion could be more suitable, particularly for patients with mechanical ventilation in the intensive care unit. In the present study, the phenobarbital blood level tended to decrease after DHP. As no comparison was made with HD and the statistical significance was not demonstrable due to the small sample size, it is difficult to make a scientific conclusion. However, given the findings in Shannon's study that DHP was comparable to HD in its clearance ability, we consider that rapid provision of DHP is a promising treatment strategy for barbiturate poisoning. Future studies should include more cases to make a comparison with HD.

In this study, DHP was carried out in patients who were in coma due to barbiturate poisoning at our hospital. However, there was no established treatment protocol, and the timing of DHP was determined by the treating physicians. This was a limitation of this study. In particular, the time from onset of coma to initial blood purification therapy as well as the timing of second DHP varied among cases. In addition, the interval of the measurement of phenobarbital blood levels without DHP varied among cases because the measurement was carried out in daily clinical practice. Furthermore, patients undergoing activated charcoal treatment and those not undergoing this treatment were included in the analysis of the change in blood levels, although activated charcoal treatment did not affect the result, as described above.

In addition, in our hospital, all patients with barbiturate poisoning were treated with DHP as blood purification therapy; therefore, a comparison with HD was not possible. Recently, Nakae *et al.* reported that selective plasma exchange with dialysis therapy using a selective membrane plasma separator, Evacure EC4A (Kawasumi Laboratories, Tokyo, Japan), can eliminate phenobarbital as effectively as

DHP.⁸ Future studies should include a comparison of this method with conventional HD and DHP.

CONCLUSION

DIRECT HEMOPERFUSION WAS useful for the treatment of phenobarbital poisoning. It decreased the blood levels of phenobarbital and might have improved the level of consciousness. As phenobarbital poisoning can cause prolonged consciousness disturbance due to its long half-life and conservative treatment is not expected to improve consciousness disturbance, rapid introduction of DHP should be considered.

FUNDING INFORMATION

THIS RESEARCH RECEIVED no specific grant from any funding agency, commercial or not-for-profit sectors.

DISCLOSURE

Approval of the research protocol: The study conformed to the provisions of the Declaration of Helsinki, and the study was approved by the Tokyo Women's Medical University Ethical Committee (Approval No. 5623).

Informed consent: All data used were within the range of usual treatment. Due to the peculiarity that all of the cases were cases of suicide attempts, consent was not obtained from the patients in this study. This has been approved by the Ethics Committee.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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