ORIGINAL ARTICLE

Effectiveness of Continuous Veno-Venous Hemofiltration and Intermittent Hemodialysis in the Treatment of Severe Acute Phenobarbital Poisoning

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Abstract

Background: Phenobarbital poisoning is common in Vietnam. The aim of this study was to compare the effectiveness of continuous veno-venous hemofiltration (CVVH) and hemodialysis (HD) on clinical outcomes in the treatment of severe acute phenobarbital poisoning.
Methods: This was a retrospective observational historically controlled study. 42 patients with severe phenobarbital poisoning were enrolled. 21 patients were treated with HD and 21 with CVVH. Both groups received similar supportive therapies consisting of mechanical ventilation, forced alkaline diuresis and multiple-dose activated charcoal.
Results: Following one course of treatment with HD (4 hours) or CVVH (~19.5 hours) the mean (SD) blood phenobarbital concentration (BPC) had decreased to 3.9 (2.5) and 3.2 (2.3) mg/dL respectively (P=0.232). Mean percentage decrease in BPC after HD and CVVH were 62.7 (12.4) and 61.5 (22.0) % respectively, showing no significant difference (P=0.782). Mean duration of coma and mechanical ventilation in CVVH group was 31.9 (26.6) and 39.7 (27.9) hours, significantly shorter than those in HD group with 66.1 (32.5) and 66.7 (32.2) hours (P=0.002; 0.001) respectively.
Conclusion: One course of treatment with CVVH and HD decreased the BPC to a similar extent but this was not associated with similar clinical outcomes. Although, CVVH was not associated with rapid fall in blood phenobarbital level, it clearly had clinical advantages by shortening the duration of coma and mechanical ventilation and with lack of coma recurrence in severe phenobarbital poisoning.

Keywords: Phenobarbital; Poisoning; Continuous Veno-Venous Hemofiltration (CVVH); Hemodialysis (HD)

INTRODUCTION

In Vietnam, poisoning with sedative medications is the leading cause of pharmaceutical poisoning accounting for 76.3% of cases (1). Of these, the majority of severe cases are due to ingestion of phenobarbital for the purpose of suicide. Large doses of phenobarbital causes very high blood phenobarbital concentration (BPC) and consequently serious complications such as loss of consciousness, deep coma, hypotension and respiratory failure may occur (2). These are major causes of death in patients with acute phenobarbital poisoning.

Most cases of mild or moderate phenobarbital poisoning can be treated with multiple-dose activated charcoal (MDAC), intravenous fluids, forced alkaline diuresis and other supportive therapies (3,4). However, in cases of life-threatening phenobarbital poisoning, extracorporeal techniques including hemodialysis (HD) and continuous veno-venous hemofiltration (CVVH) can be used for enhanced elimination in order to decrease the duration of hospitalization and complications (4-7). HD is proven to be effective in the treatment of phenobarbital poisoning, but use of this procedure is complicated in patients with hypotension. Successful use of continuous veno-venous hemodiafiltration (CVVHDF), which is a similar method to CVVH, for a severely phenobarbital poisoned patient with hypotension, was reported by Lal et al. (8). Therefore, CVVH has been regarded as an alternative modality with better safety potentials.

At Bach Mai Poison Control Center in Vietnam, severely phenobarbital poisoned patients with high BPC are treated by supportive therapies and HD or CVVH. The aim of this study was to investigate the differences in clinical outcomes between CVVH and HD in the treatment of severe acute phenobarbital poisoning.

METHODS

Study Design

This was a retrospective observational historically controlled study. 42 severely phenobarbital poisoned patients who were admitted to Bach Mai Poison Control Center during 2003-2010 were enrolled. Criteria for

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exclusion were concurrent poisoning with other sedatives and coma due to other reasons.

Indications for commencing the treatments were acute phenobarbital poisoning with BPC above 4 mg/dL and/or deep coma with stage 3 or 4. Coma was graded according to following definitions (1,9):

Stage 1. Responsive to painful but not to verbal stimulus

Stage 2. Unresponsive to all stimuli but normal reflexes and vital signs

Stage 3. Unresponsive, areflexic, stable vital signs except hypoventilation

Stage 4. Unresponsive, areflexic and unstable vital sign

Patients were categorized into 2 groups. Group 1 (study group) included 21 patients presenting between 2006 and 2010 who were treated with CVVH. Group 2 (control group) included 21 patients presenting between 2003 and 2005 who were treated with HD. Both groups received similar supportive therapies consisting of mechanical ventilation, forced alkaline dieresis and MDAC.

Intubation and mechanical ventilation were performed for all patients. Criteria for weaning off from mechanical ventilation were regaining consciousness up to Glasgow coma scale (GCS) over 13, no respiratory compromise, pCO2 less than 40 mmHg and pO2 over 85 mmHg. Criterion for stopping CVVH was regaining consciousness with GCS over 13. Hypotension was defined as systolic blood pressure below 90 mmHg.

Study facilities

CVVH: Prismaflex (Gambro) machine with Hemoselect 0.5 L filter and Diapact (B-Braun) machine with Diacap Acute filter were used. Blood flow rate was 150-180 mL/min and replacement fluid rate was 35-45 mL/kg/h. The anticoagulant used was heparin.

HD: Artificial kidney machine AK95 with polyflux 14 L filter was used. Blood flow rate was 180 mL/min and dialysate flow rate was 500 mL/min. The anticoagulant used was heparin.

BPC: Blood phenobarbital concentration was measured with HP Agilent 6310 Ion Trap LC/MS systems using HPLC/MS method.

Ethics

This study was one part of a research project approved by the ethical and scientific committees of Bach Mai hospital and Ministry of Health of Vietnam.

Data analysis

Fischer Exact test was done for ratio comparison. Mann Whitney test and Sign test were done for comparison of percentage and continuous variables. Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) was used for data analysis. $P<0.05$ was considered as significant.

RESULTS

Demographic

Of 42 patients, 26 (61.9%) were males and the average age was 34.4 (15.1) ranging from 13 to 77 years. Most cases (95.2%) were due to self-poisoning. All patients were in deep coma (stage 3-4). Mean duration of procedure with CVVH was 19.5 (8.3) hours, which was approximately 15 hours longer than HD (Table 1). As it is illustrated in table 1, there were no significant differences in baseline characteristics.

BPC Changes during Extracorporeal Therapy

After 4 hours of treatment, mean BPC in HD group was 3.9 (2.5), significantly lower than mean BPC in CVVH group with 5.4 (2.9), reflecting a quicker method to decrease BPC (Table 2). However, at the end of CVVH, BPC was

Table 1. General features of subjects before procedure

	HD	CVVH
Number of patients	21	21
Age, mean (SD)	35.9 (17.6)	32.8 (12.3)
Male/Female	1.6 (13/8)	1.6 (13/8)
GCS before procedure, mean (SD)	4.1 (1.5)	3.5 (0.9)
Stage of coma (Stage 4/total)	13/21 (59.1%)	9/21 (40.9%)
BPC before procedure (mg/dL), mean (SD)	10.1 (3.9)	8.8 (4.9)
Duration of procedure (hours), mean (SD)	4	19.5 (8.3)
Intention of Poisoning (Suicide/Total)	95.2 (20/21)	95.2 (20/21)

Table 2. Changes in blood phenobarbital concentration during procedure

BPC	HD (mg/dL), mean (SD)	CVVH (mg/dL), mean (SD)	P Value
BPC before procedure	10.1 (3.9)	8.8 (4.9)	0.134
BPC after 4 hours of procedure	3.9 (2.5)	5.4 (2.9)	0.021
BPC at the end of procedure	3.9 (2.5)	3.2 (2.3)	0.232
Decrease in BPC after 4 hours of procedure	62.7 (12.4)	36.3 (18.6)	0.001
Decrease in BPC at the end of procedure	62.7 (12.4)	61.5 (22.0)	0.782

Table 3. Comparison of Duration of coma and mechanical ventilation between two groups

	HD (hour), mean (SD)	CVVH (hour), mean (SD)	P Value
Duration of coma	66.1 (32.5)	31.9 (26.6)	0.002
Duration of mechanical ventilation	66.7 (32.2)	39.7 (27.9)	0.001

lower than what at the end of HD, though it was not significant (P=0.232). Furthermore, there was no significant difference in the percentage decrease in BPC between two groups at the end of both treatments (P=0.782).

Effectiveness and Complications of Procedures

Duration of coma and mechanical ventilation in the CVVH group were significantly shorter than the HD group (P=0.002; 0.001). Hypotension was seen at a higher proportion in HD group (23.8%) compared to CVVH group (9.5%) (Table 4). No patients suffered from hypothermia and other significant complications during procedures. Recurrence of coma was observed in two patients in HD group while none of patients in CVVH group experienced such complication. This complication occurred some hours after completion of a course of HD. Accordingly; these two patients became conscious (GCS>13) manifesting agitated after HD, but they became unconscious (GCS=7-9) again in following hours. In this respect, they did not receive any extra course of HD and they were treated supportively with mechanical ventilation and forced alkaline diuresis until getting conscious again.

Table 4. Complications of procedures

	Recurrence of coma, n (%)	Hypotension, n (%)
HD	2 (4.8)	10 (23.8)
CVVH	0	4 (9.5)

DISCUSSION

In this study, the effectiveness and complications of two extracorporeal therapies (HD and CVVH) in acute phenobarbital poisoning were investigated. Patients with phenobarbital poisoning can be treated generally with supportive care including cathartics, activated charcoal and forced alkaline diuresis (2). Although forced alkaline diuresis is a common practice in our setting, it is not advocated in most circumstances in other specialized settings (6,10). Moreover, it was shown by Mohammed-Ebid et al. that urinary alkalization compromises the effect of MDAC in phenobarbital poisoning (11).

In serious phenobarbital poisoning, HD has been used for enhanced elimination of phenobarbital in many parts of the world including Vietnam (3,4,7), but it is now infrequently performed in many developed countries (6). Moreover, effectiveness of CVVH for this indication has also been debated. In a recent study, Lee et al. showed that CVVHDF can enhance the elimination of pentobarbital (a similar compound to phenobarbital) from the circulation (12). Correspondingly, Lal et al. reported a successful use of CVVHDF for a patient with severe coma and hypotension from phenobarbital overdose (8).

Results of this study suggest that despite CVVH is a longer procedure, it is an effective method to treat acute phenobarbital poisoning and additionally it is safer than HD. Moreover, it was found that one course of HD was similarly effective on decreasing BPC compared to one course of CVVH. Nevertheless, BPC fell more quickly with HD.

Phenobarbital poisoning may cause coma and respiratory compromise (2). Hence, we considered duration of coma and mechanical ventilation to evaluate clinical effectiveness of HD and CVVH. We found that duration of coma and mechanical ventilation in CVVH group was significantly shorter than HD group, revealing CVVH is more effective. Moreover, hypotension and recurrence of coma were not observed following CVVH, implying a safer method.

It has been ascertained that many of the sedative-hypnotic medications have a redistribution phase following initial distribution (13). This is because they are dispersed and accumulated in other body tissues, especially adipose tissue (13). Therefore, after initial distribution, they reenter into blood circulation and can cause rebound manifestations. CVVH is a long extracorporeal therapy. Hence, it is capable of filtrating out the redistributed phenobarbital. Conversely, HD is a shorter technique. Therefore, redistribution of phenobarbital and as a result, recurrence of coma is more probable after HD. In these situations, extra courses of HD may solve the problem; though we treated our patients conservatively with only mechanical ventilation and forced alkaline diuresis.

LIMITATIONS

The control group in the study was retrospectively studied. Therefore, some bias could not be avoided. We suggest that future studies about comparison of elimination of BPC with CVVH and HD or CVVH and MDAC to be designed as randomized controlled trials. Moreover, in this study, BPC at the time of coma recurrence was not determined. Therefore, we propose measurement of BPC at the time of coma recurrence in routine practice and future studies. In addition, phenobarbital concentration in dialysis fluid was not measured. Thus, exact clearance of phenobarbital for both modalities could not be estimated.

CONCLUSION

One course of treatment with CVVH and HD decreased the BPC to a similar extent but this was not associated with a similar clinical outcomes. CVVH is safer and more effective than HD on treatment of severe acute phenobarbital poisoning as it shortens the duration of coma and mechanical ventilation with fewer complications. Therefore, using CVVH is recommended for treatment of severe cases of acute phenobarbital poisoning especially those with deep prolonged coma and refractory hypotension.

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Conflict of interest: None to be declared.

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REFERENCES

1. Ha NH. Study on acute medicinal poisoned patients at Hanoi Poison Control Center, Bach Mai hospital during 2002-2004

[Fellow thesis] (in Vietnamese). Hanoi: Hanoi Medical University; 2004.
2. Doyon S. Anticonvulsants. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. Goldfrank's Toxicologic Emergencies. 9th ed. New York: McGraw-Hill; 2011. p.698-710.
3. Due P. Diagnostic Criteria for Administration of Hemodialysis in Phenobarbital Poisoning (in Vietnamese). Journal of Clinical Medicine 2010 June;53:22-6.
4. Palmer BF. Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital overdose. Am J Kidney Dis 2000 Sep;36(3):640-3.
5. Jacobs F, Brivet FG. Conventional haemodialysis significantly lowers toxic levels of phenobarbital. Nephrol Dial Transplant 2004 Jun;19(6):1663-4.
6. Roberts DM, Buckley NA. Enhanced elimination in acute barbiturate poisoning - a systematic review. Clin Toxicol (Phila) 2011 Jan;49(1):2-12.
7. Winchester JF. Extracorporeal Removal of Toxic Substances. In: Brent J, Wallace KL, Burkhart KK, Phillips SD, Donovan JW, editors. Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient. 1st ed. New York: Elsevier Mosby; 2005. p.65-71.
8. Lal R, Faiz S, Garg RK, Baweja KS, Guntupalli J, Finkel KW. Use of continuous venovenous hemodiafiltration in a case of severe phenobarbital poisoning. Am J Kidney Dis 2006 Aug;48(2):e13-5.
9. Ellenhorn MJ, Barceloux DG. Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 1st ed. New York: Elsevier Science Publishing Co; 1988.
10. Proudfoot AT, Krenzelok EP, Vale JA. Position Paper on urine alkalinization. J Toxicol Clin Toxicol 2004;42(1):1-26.
11. Mohammed Ebid AH, Abdel-Rahman HM. Pharmacokinetics of phenobarbital during certain enhanced elimination modalities to evaluate their clinical efficacy in management of drug overdose. Ther Drug Monit 2001 Jun;23(3):209-16.
12. Lee JM, Lee YJ, Bang ES, Chu IS, Kim SH. Use of Continuous Venovenous Hemodiafiltration to Enhance the Elimination of Serum Pentobarbital before Diagnosis of Brain Death. J Korean Soc Transplant 2012;26(2):120-4.
13. Lee DC, Ferguson KL. Sedative-Hypnotics. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. Goldfrank's Toxicologic Emergencies. 9th ed. New York: McGraw-Hill; 2011. p.1060-71.