IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2016 Vol.:8, Issue:1

Assessment of Single and Multiple Doses of Activated Charcoal in Enhancement of Phenobarbital Clearance

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Amal Umran Mosa Alrubaee

Lecturer assistant
Department of Pharmacology and Toxicology
College of Pharmacy, University of Karbala, Iraq.

Submission: 26 November 2016
Accepted: 1 December 2016
Published: 25 December 2016

www.ijppr.humanjournals.com

Keywords: phenobarbital, activated charcoal, multiple doses, clearance

ABSTRACT

A single dose intravenous phenobarbital sodium toxicity study was conducted on Wistar albino rats followed by single and multiple doses of enteral activated charcoal through 6 hours and then plasma phenobarbital levels were assessed till 40 hours after treatment trying to compare efficacy of multiple doses with single-dose activated charcoal. Half-life was measured and drug clearances were calculated, The half-life of phenobarbital was markedly shortened with corresponding increase in plasma clearance after using single charcoal dose in comparison to phenobarbital without charcoal treatment and half-life was more shortened after treatment with multiple charcoal doses and more increase in clearance.

INTRODUCTION

Phenobarbital

Phenobarbital proprietary names are luminal; Phenobarbital Sodium; Phenobarbitone; Phenylethylmalonylurea that used in treatment of generalized tonic-clonic (grand mal) and partial seizures; sedative; may also be used for prevention and treatment of neonatal jaundice and lowering of bilirubin level in prolonged cholestasis; neonatal fit. The treatment of withdrawal symptoms in addicts of hypnotics and investigational used in febrile seizures in children [1].

Mechanism of action can be summed up by interposing transmission of impulses from the thalamus to the cortex of the brain resulting in a dissymmetry in central inhibitory and implemental mechanisms [2]. Ataxia, confusion, hypotension, hypothermia, asterixis, cognitive dysfunction, dysarthria, slurred speech, extrapyramidal reaction, unsteady gait, fever, focal neurological signs, hyporeflexia, hypothyroidism, jaundice, myocardial depression, pulmonary edema, methemoglobinemia, toxic epidermal necrolysis, gingival hyperplasia, pemphigus, bullous lesions, porphyria, ptosis, rhabdomyolysis, myoglobinuria, miosis, vision color changes (green tinge) are the signs and symptoms of phenobarbital overdose [1]

Pharmacodynamics/Kinetics:

Phenobarbital is known to be long acting barbiturates found in market. Phenobarbital half-life may reach two to seven days which is related to its low protein binding that is measured 20 to 45 %. It has an oral bioavailability of about 90%, corresponding onset of action oral administration is 20-60 minutes in comparison to 5 minutes after intravenous administration, while peak effect of intravenous administration is 30 minutes while it reached 8 to 12 hours after oral use, hydroxylation and glucuronidation are the main processes in metabolism of phenobarbital when it reaches in the liver consequently, cytochrome P450 enzymes are induced by its effect and then kidney excretes it [3],[4],[5] .

Activated Charcoal:

Treatment of oral toxicity has been treated by charcoal in active form for the bygone century or even earlier where it was used by Egyptian documented papyri to 1500 BC. It decreases systemic effects of toxins through prevention of its absorption in the alimentary tract [6] [7].

Charcoal is produced conventionally from plant matter such as coal or from natural hydrocarbons. Charcoal modified to active form by rising its temperature in oxidizing space including air, steam or carbon dioxide. Phosphoric acid is also used for charcoal activation otherwise, we can use these two methods together. This process aims to manifold the surface area from 2 to 4 m^2 /g to more than 1500 m^2 /g by creation highly developed structural pores [8].

Activated charcoal used to for human purposes. The extremely purified reaching a surface area of 2000 m^2 /g that amplify its ability to adsorb more and more toxins and improving its affinity for toxins with less molecular weight about 10 g/mol[9]. Unfortunately activated charcoal cannot adsorb few materials like heavy metals, ethanol and hydrocarbons [10].

Multiple-dose Activated Charcoal

More than one dose activated charcoal is estimated to make its advantageous effects by sticking to toxins and prevent spread from gut to circulation [11]. Toxin will pass back to gut after absorption by passive when there is difference in concentration between gut and blood with speed that differs according to gradient of concentration between the two spaces and to the surface area of diffusion expressed by gut and also relies to permeability and really to blood flow velocity. Hence, drug goes across continuously into the gut lumen where it is adsorbed to charcoal in a procedure called gastrointestinal dialysis [12], [21].

Enteroenteric circulation seen in phenobarbital toxicity is apparently disrupted by activated charcoal through many animal researchers [13] in an advocated administration orally by 0.5 to 1 g/kg[14].

Established studies in human volunteers exhibit the efficacy that is more beneficial if administered earlier within one hour of toxin consumption [15]. It is recommended that one administration of activated charcoal must be more rigorous and proposes that administration

must preserve for dangerous cases of poisoning since its risks and advantages are not well accomplished till now [16].

One of a tremendous complications of activated charcoal treatment is aspiration [17]. It is important to make sure that the airways are intact and it is crucial to secure them especially in cases with impaired brain function or respiration malfunction although it is ineffective in poisoning of alcohols and lithium and it is contraindicated in consumption of caustic materials, oils and hydrocarbons [9].

In comparison between comatose patients not secured by early intubation and patients treated with charcoal in medical centers, it seems that there is no significant difference in the hazards of aspiration, hence activated charcoal form by itself does not increase the risk of aspiration [18]. Likewise ended that the real cause of aspiration in treatment with activated charcoal is related to other elements for instance diminished level of consciousness, spontaneous emesis and seizure not because of charcoal effect [19].

Commercial charcoal powder used after it dispersed in watery field in a concentration from 10 to 20% and because that it can be rejected; thence, it is better to infuse charcoal suitable parental tubes [16].

Merigian K.S. *et al.*[20] demonstrated that activated charcoal significantly decreases vomiting rate when he compared them with another group that did not treated with charcoal in a control research as it decreased from 23% to 13% with $p < 0.01$ and also he declared a significant shortening inpatient hospital rest for those treated with charcoal.

By consumption of repeated administration exceeding twice of activated charcoal, it is considered that the difference in presence of toxin between blood and gut helps to maintain continuous passage of toxin into the lumen of alimentary tract when drugs demonstrate a prolonged release phase or when reabsorption by enterohepatic circulation of active drug or active metabolites can be forbidden [22].

Iatrogenic complications including perforation of esophagus with tube may results in mediastinitis [24] or stomach perforation causing peritonitis [25] or stercolith [26] and bezoars from repeated administration of charcoal that may end with intestinal obstruction[27] Occasionally, bowel obstruction has been reported demanding manual evacuation or surgical intervention[28] ,[29].

Repeated administration of activated charcoal could enhance gut clearance from toxins especially when their concentration reaching high levels in blood and having prolonged half-life, and when its distribution is limited [15].

Most centers recommend administration of quarter to one gram per body weight kg per single administration with time intervals between administration of two to four hours less or more according to each case supported by nasogastric tube [30]. Therefore the schedule of repeated administration of activated charcoal is adopted regardless the time till [31].

MATERIALS AND METHODS

In this study, we used 15 adult male Wistar albino rats weighted between (200-220g) obtained from animal house of Karbala university/pharmacy college which were housed in groups in plastic cages, with food and water freely available and they were kept in normally lighted environment. Rats were treated into three groups each contained 5 rats:

Group (A) (control): They were treated with intravenous phenobarbital of 10 mg /kg

Group (B): Rats were treated with intravenous phenobarbital of 10 mg /kg and after 30 minutes there were treated with single-dose activated charcoal enteral by nasogastric gavage by 1 g/kg.

Group (C): Rats were treated with intravenous phenobarbital of 10 mg /kg and then treated with multiple doses enteral activated charcoal of 1 g/KG after 30 minutes and further 0.5 mg/kg after 3 hours and 6 hours.

Blood samples were taken after 8 hours and 48 hours and phenobarbital plasma level were measured by high-performance liquid chromatography (HPLC) test at Baghdad medical city toxicology center. Half time and clearance were calculated.

We utilized Charcodote (Teva UK Ltd) Activated charcoal 200mg/1ml Charcodote 200mg/ml oral suspension (sugar-free) 250 ml.

Phenobarbitone (200 mg/ml) (Phenobarbital) from Nicholas Piramal India Ltd.

3-French soft rubber pediatric feeding tubes.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics for windows version. The gained data were analyzed by means of difference between control (group A) and others (groups B and C) as testing if there is significant difference using one-way analysis of variances (using ANOVA). Considering P-values of 0.05 or less were significant.

RESULTS

Half-life was measured and drug clearances were calculated. The half-life of phenobarbital was markedly shortened with corresponding increase in plasma clearance after using single charcoal dose (phenobarbital half-life with single activated charcoal dose = 31.54 ±3.24 hr and clearance =0.0013 ±0,00013 L/kg/hr) in comparison to phenobarbital without charcoal treatment (phenobarbital half-life without activated charcoal=36.23±4.48 hr and clearance=0.0012±0.00017 L/kg/hr) [table (2) and (4) and half-life was more shortened after treatment with multiple charcoal doses and more increase in clearance (phenobarbital half-life with multiple activated charcoal doses =16.54±1.45 hr and clearance =0.0025±0.00022 L/kg/hr) [table (1) and (2)].

Table (1) Descriptive results of phenobarbital $T_{1/2}$

Groups	Rats number	$T_{1/2}$ mean	St. deviation	Minimum	Maximum
Group A	5	36.2342	4.47982	29.35	40.41
Group B	5	31.5488	3.14279	28.05	35.53
Group C	5	16.5454	1.45490	15.21	18.50

Table (2) Descriptive results of Phenobarbital clearance

Groups	Rats number	Clearance mean	St. deviation
Group A	5	0.0012	0.00017
Group B	5	0.0013	0.00013
Group C	5	0.0025	0.00022

The comparison of clearance of group C with group A [table (3)] show highly significant increase that p is less than 0.001 with corresponding highly significant shortened half-life that P is less than 0.001 fig (1).

Table (3) Multiple comparisons between groups by $T_{1/2}$ mean difference significance

Group comparisons	Mean differences	Significant
Group A with B	4.68548	0.043
Group A with C	19.68880	<0.001
Group B with C	15.00332	<0.001

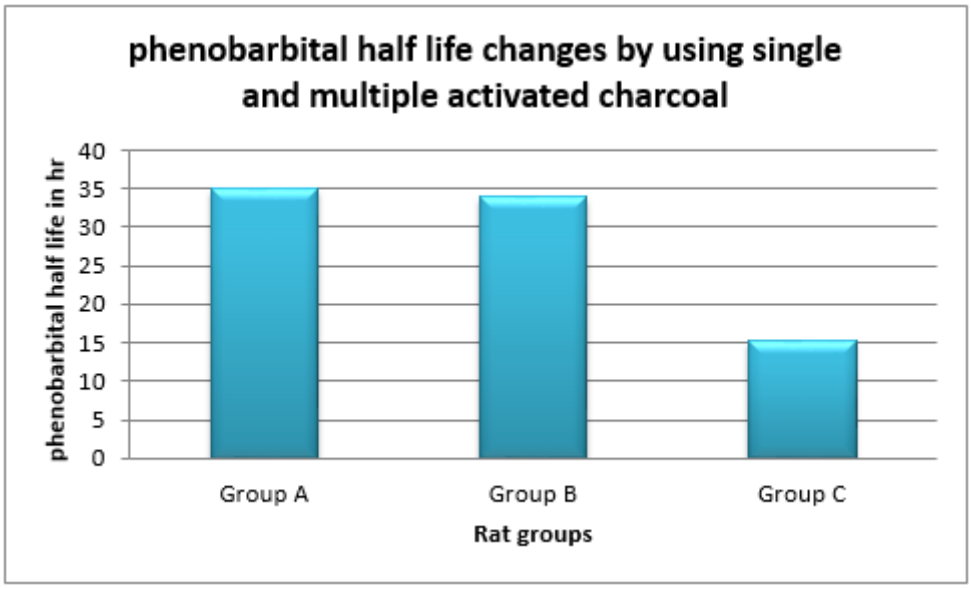

Figure (1) Phenobarbital half-life changes between groups

The comparison of clearance of group C with group B [table (4)] shows highly significant increase that p is less than 0.001 with corresponding highly significant shortened half-life that p is less than 0.001 fig (2).

Table (4) Multiple comparisons between groups by clearance mean difference significance

Group comparisons	Mean differences	Significant
Group A with B	0.00018	0.133
Group A with C	0.00138	<0.001
Group B with C	0.00120	<0.001

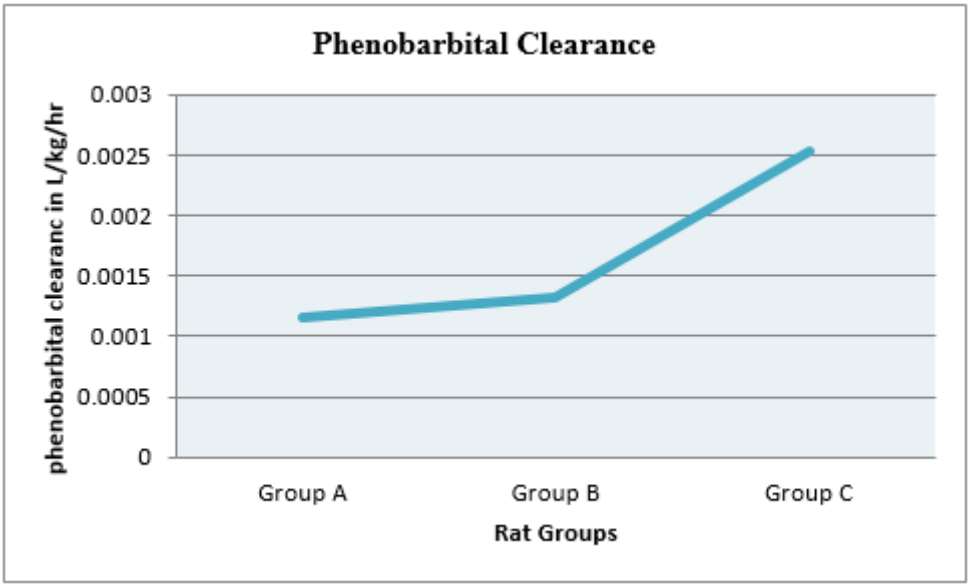

Figure (2) Comparison of phenobarbital clearance between groups

DISCUSSION

Administration of multiple-dose activated charcoal in phenobarbital poisoning considerably reduces serum phenobarbital and enhances clearance compared with control group and it is more effective than single-dose charcoal, on the basis that repeated administration of activated charcoal will bring the toxin to reenter gut after absorption by passive diffusion when its concentration in blood is greater than gut [21] hence it prevent its reabsorption and multiple doses acts to maintain charcoal level in the gut.

Although Kornberg A. E et al.[23] could not reach the greatest effect of charcoal administration in a genuine clinical research, our results can help understand charcoal efficacy. Our study outcomes are in agree with Arimori and Nakano where there was significant reduction in phenobarbital half-life achieving p-value of 0.05 where half-life changed from 8.52 ± 0.62 hours into 5.71 ± 0.35 hours and on the other hand a significant increment in phenobarbital clearance of p-value 0.01 where it changed from 50.2 ± 2.73 to 77 ± 1.21 ml/kg/ hour [32].

In a clinical study, large charcoal doses are given resulted in a great reduction of time that the patient to be recover from poisoning through enhancement of toxin clearance [33].

In another research applied on neonates admitted because of severe central nervous system impairment after phenobarbital treatment, repeated administration of activated charcoal

reduced phenobarbital half-life from measured 250 hours to 22 hours and improve brain stem functions [34].

CONCLUSION

Activated charcoal has been used in poisoning for many years. It has a relatively low incidence of side effects. The phenobarbital half-life was obviously decreased with corresponding increase in plasma clearance after using single charcoal dose in comparison to phenobarbital without charcoal treatment and half-life was more shortened after treatment with multiple charcoal doses and more increase in clearance.

Although there are other effective procedures like hemodialysis and hemoperfusion, repeated administration of activated charcoal is still a valuable method in treatment of poisoning in cautious practice by putting in mind expected complications.

REFERENCES

1- Ali FE, Al-Bustan MA, Al-Busairi WA, *et al*, ‘‘Loss of Seizure Control Due to Anticonvulsant-Induced Hypocalcemia,’’ Ann Pharmacother, 2004, 38(6):1002-5.
2- Kawasaki CI, Nishi R, Uekihara S, *et al*, ‘‘How Tightly Can a Drug Be Bound to a Protein and Still Be Removable by Charcoal Hemoperfusion in Overdose Cases?’’ Clin Toxicol (Phila) , 2005, 43(2):95-9.
3- Cingolani M, Cippitelli M, Froldi R, *et al*, ‘‘Stability of Barbiturates in Fixed Tissues and Formalin Solutions,’’ J Anal Toxicol, 2005, 29(3):205-8.
4- Shalkham AS, Kirrane BM, Goldfarb D, *et al*, ‘‘The Availability and Use of Charcoal Hemoperfusion in the Treatment of Poisoned Patients,’’ Clin Toxicol (Phila), 2005, 43:676.
5- Ebid A-HIM, Abdel-Rahman HM. Pharmacokinetics of phenobarbital during certain enhanced elimination modalities to evaluate their clinical efficacy in management of drug overdose. Therapeutic Drug Monitoring 2001; 23(3):209–216.
6- Watson W, Litovitz TL, Klein-Schwartz W, Rodgers GC, Youniss J, Reid N, *et al*. 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med. 2004; 22: 335-404.
7-Historical production and use of carbon materials. http://www.caer.uky.edu/ carbon/history/carbonhistory.shtml. [Accessed 26 October 2006]
8- Park GD, Spector R, Goldberg MJ, Johnson GF, Feldman R, Quee CK. Effect of the surface area of activated charcoal on theophylline clearance. *J Clin Pharmacol* 1984; 24:289–292.
9- Krenzelok EP, Vale JA, Chyka PA, Seger D. AACT/EAPCCT position paper: single-dose activated charcoal. J Toxicol Clin Toxicol. 2005;43: 61-87.
10- Erickson TB. Toxicology: ingestions and smoke inhalations: APLS. In: Gausche-Hill M, Fuchs S, Yamamoto L, editors. The pediatric emergency resource. 4th ed. Massachusetts: Jones and Bartlett; 2004. p. 239.
11- McKinnon RS, Desmond PV, Harman PJ, *et al*. Studies on the mechanisms of action of activated charcoal on theophylline pharmacokinetics. *J Pharm Pharmacol* 1987; 39:522–525.
12- Levy G. Gastrointestinal clearance of drugs with activated charcoal. *New Engl J Med* 1982; 307:676–678.
13- Wakabayashi Y, Maruyama S, Hachimura K, Ohwada T. Activated charcoal interrupts enteroenteric circulation of phenobarbital. *J Toxicol Clin Toxicol* 1994; 32: 419–424.
14- Gaudreault P. Activated charcoal revisited. Clin Ped Emerg Med 2005; 6:76–80.
15- Krenzelok EP. New developments in the therapy of intoxications. Toxicol Letters. 2002; 127:299-305.
16- Seger D. Single-dose activated charcoal-backup and reassess. J Toxicol Clin Toxicol. 2004; 42:101-10.
17- Heard K. The changing indications of gastrointestinal decontamination in poisoning. Clin Lab Med 2006; 26:1–12.

18- Liisanantti J, Paivi K, Matti M. Aspiration pneumonia following severe selfpoisoning. Resuscitation 2003; 56:49–53.
19- Isbister GK, Downes F, Sibbritt D. Aspiration pneumonitis in an overdose population: frequency, predictors, and outcomes. Crit Care Medv2004; 32:88–93.
20- Merigian KS, Blaho KE. Single-dose oral activated charcoal in the treatment of the self-poisoned patient: a prospective, randomized, controlled trial. Am J Therapeut 2002; (9):301–308.
21- Vale JA, Krenzelok EP, Barceloux GD. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. Clin Toxicol 1999; 37:731–751
22- Tenenbein M. Multiple doses of activated charcoal: time for reappraisal II. Ann Emerg Med 2003; 42:597–598.
23- Kornberg AE, Dolgin J. Pediatric ingestions: charcoal alone versus ipecac and charcoal. Ann Emerg Med 1991; 20:648–651.
24- Caravati EM, Knight HH, Linscott MS Jr. Esophageal laceration and charcoal mediastinum complicating gastric lavage. J Emerg Med 2001; 20:273–276
25- Mariani PJ, Pook N. Gastrointestinal tract perforation with charcoal peritoneum complicating orogastric intubation and lavage. Ann Emerg Med 1993; 22:606–609.
26- Gomez HF, Brent JA, Munoz DC IV. Charcoal stercolith with intestinal perforation in a patient treated for amitriptyline ingestion. J Emerg Med 1994; 12:57–60.
27- Chan JC, Saranasuriya C, Waxman BP. Bezoar causing small bowel obstruction after repeated activated charcoal administration. Med J Aust 2005; 183:537.
28- Osterhoudt KC, Durbin D, Alpern ER, Henretig FM. Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. Pediatrics 2004; 113:806–810.
29- Arimori K, Kawano H, Nakano M. Gastrointestinal dialysis of disopyramide in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1989; 27:280–284.
30- AACT/EAPCCT position statement and practical guidelines on the use of multiple dose-activated charcoal in the treatment of acute poisoning. J Toxicol Clin Toxicol. 1999; 37:731-51.
31- Chyka PA, Seger D, Krenzelok EP, Vale JA, American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists Position paper: single-dose activated charcoal. J Toxicol Clin Toxicol. 2005; 43:61–87.
32-Arimori K, Nakano M. Accelerated clearance of intravenously administered theophylline and phenobarbital by oral doses of activated charcoal in rats. A possibility of the intestinal dialysis. *J Pharmacobiodyn* 1986; 9:437–441.
33-Boldy DAR, Vale JA, Prescott LF. Treatment of Phenobarbitone poisoning with repeated oral administration of activated charcoal. *Q J Med* 1986; 61:997–1002.
34-Veerman M, Espejo MG, Christopher MA, Knight M. Use of activated charcoal to reduce elevated serum phenobarbital concentration in a neonate. *J Toxicol Clin Toxicol* 1991; 29:53–58