Effect of Activated Charcoal in Reducing Paracetamol Absorption at a Supra-Therapeutic Dose

Winai Wananukul MD*, Supranee Klaikleun MD*,
Charuwan Sriapha BSc*, Achara Tongpoo BSc*

** Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Background: *Activated charcoal (AC) is recommended for treatment of acute poisoning, thereby decreasing gastrointestinal tract absorption. AC from different sources may have different adsorptive capacity. The AC that is available in Thailand has not been proven yet for its efficacy. The authors simulated paracetamol overdose model for the present study.*
Objective: *To assess the efficacy of AC that is available in Thailand in decreasing absorption of paracetamol at supra-therapeutic dose.*
Material and Method: *This was a two-arm, prospective, crossover study. Washout period was 1 week. Twelve healthy male volunteers participated. All volunteers were randomly assigned to either sequence of control-experiment (CE) or EC. The participants ingested 60 mg/Kg of paracetamol at Time = 0. At Time = 0.25 hour, they ingested 50 g of AC as slurry with 250 ml of water when they were assigned as E, but drank 250 mL of water when were assigned as C. Blood samples were serially collected for determination of paracetamol concentration and calculating pharmacokinetic parameters, area under the time-concentration curve (AUC (0,∞)).*
Results: *Means of the AUC (0,∞) were 313.7 $\pm$ 29.8 and 184.8 $\pm$ 91.6 mg-h/L in the control and experimental arm, respectively. It was statistically different (p = 0.01).*
Conclusion: *The tested AC was found to be able to reduce the absorption of the supratherapeutic dose of paracetamol.*

Keywords: *Activated charcoal, Paracetamol, Acetaminophen, Overdose, Decontamination, Randomization, Cross-over, Pharmacokinetics*

J Med Assoc Thai 2010; 93 (10): 1145-9
Full text. e-Journal: *http://www.mat.or.th/journal*

Gastrointestinal decontamination is an initial step in treating poison exposure patients. Sufficient gastrointestinal decontamination can reduce poison absorption, risk of developing systemic toxicity and clinical severity. Thus, it improves medical outcome[1]. Single dose of activated charcoal is a common method for gastrointestinal decontamination. It is widely recommended for treating poison ingestion patients[2]. According to the position statement by American Academy of Clinical Toxicology and European Association of Poison Centers and Clinical Toxicologist in 2005, a single dose of activated charcoal is recommended for patients who ingest toxic amount of poison within 1 hour. The dosage regimen is 0.5-1.0 gram/kg in children and 25-100 gram in adults[3].

Correspondence to:
Wananukul W, Department of Medicine, Ramathibodi Poison Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.
Phone & Fax: 0-2201-1086
E-mail: rawwn@mahidol.ac.th

Activated charcoal can absorb toxic substances in the gastrointestinal tract and prevent their absorption into the circulation. The adsorptive capacity of activated charcoal depends on many factors including physicochemical properties of activated charcoal, solubility and pH of toxic substances and presence of gastric content[4]. Physicochemical properties include particle size, pore size and surface area of the activated charcoal. No relevant evidence has been demonstrated for the clear influence of any single physicochemical property of activated charcoal on its adsorptive capacity[5].

Charcoal can be derived from many substances such as coconut shell, peat, lignite, and wood. Then, it is activated by heating in hot stream or air. The activation process causes the charcoal to become small size particles with an internal pore structure. Different kinds of activated charcoal, which are from different productions, have different physicochemical properties and different adsorptive capacity[6,7].

The British Pharmacopiea (BP) and the United States Pharmacopiea (USP) specify only that medicinal activated charcoal must meet standards for adsorption, contamination and purity[3]. The surface area typically ranges from 950-2,000 m^2/g. Other physicochemical properties are not defined. In Thailand, there is only one preparation of activated charcoal available for clinical use. It has been declared that its surface area is more than 1,000 m^2/g, with particle size less than 75 mm.

Paracetamol is the most common drug poisoning in Thailand and over the world[8-10]. Its toxicity is dose-dependent. Paracetamol at the dose of more than 150 mg/kg has been reported to have association with risk of developing hepatotoxicity. In clinical practice, plasma paracetamol concentration is the best predictor of its toxic severity. Several clinical studies of activated charcoal in reducing drug absorption in healthy volunteers are documented. Paracetamol is a common drug, which is used for this purpose[3]. Doses of paracetamol in the studies vary widely, ranging from 20 to 80 mg/kg. In the present study, the authors designed a model of supra-therapeutic dose of paracetamol for evaluating the efficacy of the activated charcoal in reducing paracetamol absorption from the gastrointestinal tract in man.

Material and Method

The present study was a randomized design, prospective, two-arm crossover trial in healthy volunteers. The protocol was approved by the Ethics Committee on Human Experimentation of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The primary outcome parameter for indicating paracetamol absorption and the effect of activated charcoal was the total area under the curve between paracetamol concentration and time to infinity (AUC $(0,\infty)$.

Study design

The eligible volunteers must be persons who had normal physical examination, normal laboratory tests for liver and kidney functions, and were not regular alcohol drinkers. They gave written informed consent before participating in the present study. They were also instructed to avoid any kind of alcoholic beverages before and during the present study. The number of sample size[12] was form the recommended number by the Thai FDA for bioequivalence study.

In this 2-arm crossover study, the experiment arm was activated charcoal (E) and the control (C) arm was water. All volunteers were randomly assigned to either sequence of CE or EC. Washout period was 1 week.

On each occasion, the volunteers were fasted overnight. Volunteers in both arms ingested 60 mg/kg of paracetamol at T = 0. At the T = 0.25 hour, the volunteers in the experiment arm ingested 50 gram of the tested activated charcoal as slurry with 500 ml of water, and those in the control arm drank 500 ml of water. Food was served at 4 hours after having taken paracetamol. Blood samples were serially collected via heparinized catheter at T = 0, 0.25, 0.5, 0.75, 1, 2, 4, 8 and 12 hours. The plasma paracetamol concentrations were measured by High Performance Liquid Chromatography.

The plasma paracetamol concentrations of each volunteer were plotted against the time for each experimental occasion. Pharmacokinetic variables of paracetamol were calculated by using the WinNonlin (standard version 2) pharmacokinetic program. The total area under the curve between paracetamol concentration and time to infinity (AUC $(0,\infty)$), maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax) and elimination half-life ($T_{1/2}$) were calculated. The AUC $(0,\infty)$ of each arm was calculated and expressed as mean, whereas other pharmacokinetic parameters in each experimental arm were expressed as median.

Statistical analyses

All statistical analyses were performed by using Strata version 10, and probabilities used the two-tail test and a value of $p \leq 0.05$ was the statistically significant level. The authors tested the difference of AUC $(0,\infty)$ between the control arm and experimental arm by paired t-test. The differences of other pharmaco-kinetic parameters (Cmax, Tmax and $T_{1/2}$) between the experimental arm and control arm were tested by Wilcoxon Signed Ranks test. The period effect and carry-over effect was tested by Mann-Whitney U test.

Results

Twelve healthy male volunteers participated in the present study. All of them participated in both arms. None had withdrawn during the present study.

Mean paracetamol concentrations in both experimental arms. The plasma paracetamol concentrations of the activated charcoal treatment arm were lower than those of the control arm at most of the time points. Pharmacokinetic parameters of both arms are shown in Table 1.

Table 1. Effect of activated charcoal (50 gram) on paracetamol (60 mg/kg) absorption, comparing area under the curve, Cmax, Tmax and $t^{1/2}$ of control arm with and activated charcoal arm (n = 12)

	Control	Activated charcoal	% reduction
AUC (0-∞) (mg-h/L)	313.7 ± 29.8*	184.8 ± 91.6*	40.9 ± 29.1
Cmax*** (mg/L)	71.0**	48.7**	35.9
Tmax*** (h)	0.5**	0.25**	50.0
$T_{1/2}$*** (h)	3.0**	3.1**	-3.8

* p = 0.01 (paired t-test)
** p > 0.05 (Wilcoxon Signed Ranks test)
*** Results are expressed as median

As a primary outcome, AUC (0,∞) of the activated charcoal arm was significantly different from that of the control arm (p = 0.002). The effect of activated charcoal on AUC (0,∞) reduction was 40.9% from the control arm (Table 1). Neither the period effect nor carry-over effect was found.

The medians $T_{1/2}$ of both arms were not statistically significantly different. The difference between the $T_{1/2}$ of both arms was only 3.8% (Table 1). Therefore, a single dose of activated charcoal treatment did not have any effect on $T_{1/2}$.

The pharmacokinetic parameters of paracetamol, Cmax and Tmax, of the activated charcoal arm were lower than those of the control arm, though there were not statistically significantly different. In the activated charcoal treatment arm, the Cmax was reduced by 35.9% and Tmax reduction was 50.0% (Table 1). There was high variability and without any statistical significance.

As for the compliance, all of the volunteers were able to take the activated charcoal without vomiting. No adverse effect was detected during and after the present study.

Discussion

Both drug absorption and clearance determine the AUC. The drug clearance is inversely correlated with $T_{1/2}$. In the present study, the $T_{1/2}$ of both arms were not different. The clearance of paracetamol did not change by single dose of activated charcoal, though multiple doses of activated charcoal increase the clearance[11]. Thus, the changes of AUC in the present study were mainly determined by drug absorption. This model was appropriate for evaluating the effect of activated charcoal on paracetamol absorption. The present study showed that administering 50 g of activated charcoal at 15 minutes after taking supra-therapeutic dose of paracetamol (60 mg/kg) was able to reduce the absorption of paracetamol by 40.9%. Previous studies have shown that reduction of paracetamol AUCs range from 25-85%[8,12-18] if the activated charcoal is administered within 60 minutes after paracetamol ingestion, as summarized in Table 2. Therefore, the magnitude of AUCs reduction in the present study was compatible with the others. The percent reduction is likely to be of clinical relevance. Therefore, the activated charcoal, which is available in Thailand, has an efficacy to adsorb paracetamol and to partially prevent paracetamol absorption from the gastrointestinal tract into the circulation.

The authors are well aware that pharmacokinetics of paracetamol in an overdose setting may be different from that of therapeutic dose. Doses of paracetamol, which have been used for simulating overdose, ranges 20 to 80 mg/kg. Because it is limited by an ethical issue and volunteer safety, we decided to use only as high as 60 mg/kg of paracetamol in this study. The authors are also aware that the efficacy of activated charcoal to prevent gastrointestinal absorption is time dependent. The beneficial effect of activated charcoal is well demonstrated if it is administered within 60 minutes after ingestion. The objective of the present study was to demonstrate the efficacy of tested activated charcoal. If the time point of administering activated charcoal was relatively late, the authors might not be able to demonstrate its effect. Thus, as early as 15 minutes after paracetamol ingestion was the time point for administering activated charcoal. However, it is not relevant in a common clinical setting. Therefore, the present finding is to be interpreted cautiously. The present study may be the initial step for evaluating the efficacy of activated charcoal.

A dose of 50 g of activated charcoal is palatable and does not produce any serious adverse effects. The tested activated charcoal may have

Table 2. Summary of randomized controlled trials on the efficacy of activated charcoal on paracetamol absorption at various doses of paracetamol, by various types of activated charcoal and time of its administration

Number of volunteers	Dose of paracetamol (mg)	Activated charcoal		% reduction (AUC)	Ref.
		Time of administration (min)	Surface area (m^2/g)		
8	1,000	0	900-1,500	36.9*	[12]
5	1,000	0	900-1,500	61.4*	[13]
8	80 mg/kg	0	unknown	74.2	[14]
6	1,000	5	1,600-2,000	85	[16]
12	60 mg/kg	15	1,000	40.9	This study
5	1,000	30	900-1,500	31.1*	[13]
6	1,000	30	1,600-2,000	40	[15]
10	3,000	60	900-1,500	25.5	[16]
10	3,000	60	unknown	43	[17]
10	4,000	60	unknown	30.5	[18]

* Calculated from urinary excretion of paracetamol

the same efficacy and safety as the international formulation. Therefore, the activated charcoal should be used as gastrointestinal tract decontamination agent for treating paracetamol overdose in the early phase. By extrapolation, the activated charcoal should be used for some other but not all toxic substances[3].

In conclusion, the authors have demonstrated the efficacy of the activated charcoal in reducing gastrointestinal absorption of the supra-therapeutic dose of paracetamol. The activated charcoal is safe and should be administered early in treating human poison ingestion.

.

Acknowledgment

This work was supported by the Faculty of Medicine Ramathibodi Hospital, Mahidol University. The authors wish to thank Associate Professor Korbtham Sathirakul, Department of Pharmacy, Faculty of Pharmacy, Mahidol University for pharmacokinetic analysis, Mrs. Umaporn Udomsubpayakul, Clinical Epidemiology and Biostatistics Unit, Research Center, Faculty of Medicine Ramathibodi Hospital, and Professor Amnuay Thithapandha for editing the manuscript.

References

1. Greene S, Harris C, Singer J. Gastrointestinal decontamination of the poisoned patient. Pediatr Emerg Care 2008; 24: 176-86.
2. Houston M, Hendrickson RG. Decontamination. Crit Care Clin 2005; 21: 653-72, v.
3. Chyka PA, Seger D, Krenzelok EP, Vale JA. Position paper: Single-dose activated charcoal. Clin Toxicol (Phila) 2005; 43: 61-87.
4. Cooney D. Activated charcoal in medicinal applications. New York: Marcel Dekker; 1995.
5. Watson WA. Factors influencing the clinical efficacy of activated charcoal. Drug Intell Clin Pharm 1987; 21: 160-6.
6. al Shareef AH, Buss DC, Routledge PA. Drug adsorption to charcoals and anionic binding resins. Hum Exp Toxicol 1990; 9: 95-7.
7. McFarland AK III, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. Ann Pharmacother 1993; 27: 358-61.
8. Perkins JD. Acetaminophen sets records in the United States: number 1 analgesic and number 1 cause of acute liver failure. Liver Transpl 2006; 12: 682-3.
9. Wananukul W, Sriapha C, Tongpoo A, Sadabthammarak U, Wongvisawakorn S, Kaojarern S. Human poisoning in Thailand: The Ramathibodi Poison Center's experience (2001-2004). Clin Toxicol (Phila) 2007; 45: 582-8.
10. Hawton K, Bergen H, Casey D, Simkin S, Palmer B, Cooper J, et al. Self-harm in England: a tale of three cities. Multicentre study of self-harm. Soc Psychiatry Psychiatr Epidemiol 2007; 42: 513-21.
11. Chyka PA, Holley JE, Mandrell TD, Sugathan P. Correlation of drug pharmacokinetics and effectiveness of multiple-dose activated charcoal therapy. Ann Emerg Med 1995; 25: 356-62.

12. Galinsky RE, Levy G. Evaluation of activated charcoal-sodium sulfate combination for inhibition of acetaminophen absorption and repletion of inorganic sulfate. J Toxicol Clin Toxicol 1984; 22: 21-30.
13. Levy G, Houston JB. Effect of activated charcoal on acetaminophen absorption. Pediatrics 1976; 58: 432-5.
14. Rangan C, Nordt SP, Hamilton R, Ingels M, Clark RF. Treatment of acetaminophen ingestion with a superactivated charcoal-cola mixture. Ann Emerg Med 2001; 37: 55-8.
15. Neuvonen PJ, Vartiainen M, Tokola O. Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. Eur J Clin Pharmacol 1983; 24: 557-62.
16. McNamara RM, Aaron CK, Gemborys M, Davidheiser S. Efficacy of charcoal cathartic versus ipecac in reducing serum acetaminophen in a simulated overdose. Ann Emerg Med 1989; 18: 934-8.
17. Yeates PJ, Thomas SH. Effectiveness of delayed activated charcoal administration in simulated paracetamol (acetaminophen) overdose. Br J Clin Pharmacol 2000; 49: 11-4.
18. Green R, Grierson R, Sitar DS, Tenenbein M. How long after drug ingestion is activated charcoal still effective? J Toxicol Clin Toxicol 2001; 39: 601-5.

ประสิทธิภาพของผงถ่านกัมมันต์ในการลดการดูดซึมยาพาราเซตามอลในขนาดสูง

วินัย วนานุกูล, สุปราณี คล้ายเคลื่อน, จารุวรรณ ศรีอาภา, อัจฉรา ทองภู

ภูมิหลัง: *การใช้ผงถ่านกัมมันต์เป็นขั้นตอนหนึ่งของการรักษาผู้ป่วยที่ได้กินสารพิษ เพื่อลดการดูดซึมของสารพิษที่จะเข้าร่างกาย ผงถ่านที่ใช้เพื่อวัตถุประสงค์นี้มีการกำหนดคุณสมบัติให้อย่างคร่าว ๆ ในประเทศไทย มีผงถ่านที่ระบุไว้เพื่อใช้ในจุดประสงค์ชนิดเดียว แต่ไม่มีการศึกษาประสิทธิภาพของผงถ่านชนิดนี้ การศึกษานี้ใช้ภาวะการกินยาพาราเซตามอลในขนาดสูงกว่าขนาดปกติเพื่อการศึกษาประสิทธิภาพของผงถ่านกัมมันต์*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของผงถ่านกัมมันต์ที่มีในประเทศไทย ในการลดการดูดซึมของยาพาราเซตามอล ที่ขนาดสูง (60 มก./ กก.)*

วัสดุและวิธีการ: *การศึกษาเป็นแบบ prospective, randomized- assigned crossover โดยมี washout period 1 สัปดาห์ อาสาสมัครเป็นชาย 12 คน การศึกษาแบ่งเป็น 2 แบบคือ กลุ่มควบคุม (C) และกลุ่มทดลอง (E) อาสาสมัครแต่ละคนจะถูกเลือกแบบสุ่มให้มีลำดับการศึกษาเป็น CE หรือ EC เมื่อเริ่มการศึกษาแต่ละครั้งอาสาสมัครจะกินพาราเซตามอลขนาด 60 มก./กก. ที่เวลา = 0 อาสาสมัครที่ถูกจัดให้อยู่ในกลุ่มทดลองในครั้งนั้นจะดื่มน้ำ 250 มล. ที่เวลาเท่ากับ 0.25 ชั่วโมง ส่วนอาสาสมัครที่อยู่ในกลุ่มทดลองจะกินผงถ่านกัมมันต์ 50 กรัม ผสมน้ำ 250 มล. มีการเก็บเลือดเป็นระยะเพื่อหาระดับยาพาราเซตามอล ระดับยาของอาสาสมัคร จะถูกนำไปคำนวณหาค่าเภสัชจลนศาสตร์เพื่อหาค่า AUC (0, ∞)*

ผลการศึกษา: *ค่าเฉลี่ยของ AUC ในกลุ่มควบคุมและกลุ่มทดลองเท่ากับ 313.7 ± 29.8 และ 184.8 ± 91.6 มก. ชั่วโมง/ลิตร ตามลำดับซึ่งแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p = 0.01$)*

สรุป: *ผงถ่านกัมมันต์ที่ทำการศึกษาสามารถลดการดูดซึมยาพาราเซตามอลในขนาดสูงเข้าสู่ร่างกายได้*