Paraxanthine/Caffeine Ratio : As an Index for CYP1A2 Activity in Polycyclic Aromatic Hydrocarbons Exposed Subjects

SUPEECHA WITTAYALERTPANYA, MSc*,
YAOWARAT HINSUI, MSc*,
SOMSONG LAWANPRASERT, PhD**

Abstract

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous in the environment and originate from incomplete combustion process of organic materials. These compounds are bioactivated to reactive metabolites which bind covalently to DNA and subsequently initiate carcinogenesis. PAHs have been well established as an enzyme inducer of cytochrome P450 (CYP) such as CYP1A1 and CYP1A2. Caffeine is primarily metabolized by CYP1A2 to paraxanthine, so it has been used as a specific probe for assessing CYP1A2 activity. The purpose of this study was to compare CYP1A2 activity in female subjects that were automobile exhaust exposed and non-automobile exhaust exposed using serum paraxanthine/caffeine ratio as an index. Each subject took a 180 mg single oral dose of caffeine solution. Blood samples were collected before and 5 hours after caffeine intake. Serum samples were separated by centrifugation and stored at -20°C until analysis by high performance liquid chromatography (HPLC). Carbon monoxide (CO) level in blood was also detected using spectrophotometer. The results showed that serum paraxanthine/caffeine ratio in exposed subjects was significantly higher than non-exposed subjects (mean ± SE of 0.45 ± 0.05 and 0.33 ± 0.03, respectively; $p < 0.05$). CO level in exposed subjects was also significantly higher than non-exposed subjects (mean ± SE of 4.03 ± 0.21 and 3.01 ± 0.18, respectively; $p < 0.05$). Conclusion: Paraxanthine/caffeine ratio, as an index for CYP1A2 activity, can be used to determine PAHs exposure. Automobile exhaust exposed subjects demonstrated significantly higher CYP1A2 activity than that of the non-exposed subjects. Exposed subjects have a possibly higher risk of chemical carcinogenesis.

Key word : Paraxanthine/Caffeine Ratio, CYP1A2, PAHs

WITTAYALERTPANYA S, HINSUI Y, LAWANPRASERT S
J Med Assoc Thai 2003; 86 (Suppl 2): S310-S317

* Department of Pharmacology, Faculty of Medicine,
** Department of Pharmacology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds with two or more fused aromatic rings[1]. They are produced during the incomplete combustion process of organic materials such as natural gas, coal, coal tar and petroleum, etc[2,3]. They are also found contaminated in tobacco smoke, automobile exhaust and dietary sources [4,5]. Entering the body, PAHs undergo hepatic metabolic activation resulting in reactive intermediates that could bind covalently to DNA. The hepatic enzyme involving the biotransformation of these compounds include CYP1A1, epoxide hydroxylase, CYP 3A4 and other enzymes[6]. Direct covalent binding of the reactive metabolites of PAHs to DNA to produce carcinogen DNA adducts is an essential step in cancer development[7]. PAHs have been well established as an enzyme inducer of the cytochrome P4501A (CYP1A) family, CYP1A1 and CYP1A2[3,8,9]. The mechanism of induction by these compounds has been intensively investigated[10].

CYP1A2 is normally expressed in human liver, accounting for 15 per cent of the total P450 content[11]. This isoform of CYP in the metabolism of many drugs such as theophylline, caffeine[9], clozapine[12], propanolol[13], imipramine and tracrine[14]. In addition, human CYP1A2 plays an important role in the activation of environmental procarcinogens such as aromatic amines, heterocyclic amines and aflatoxin B1, to reactive intermediates that cause colorectal or bladder cancers[15,16]. Activity of CYP1A2 is influenced by both internal factors and external factors. Internal factors include age, race and gender [17]. External factors include enzyme inducers such as omeprazole[18], cigarette smoking[19] and enzyme inhibitors such as oral contraceptive[20], cimetidine [21], alcohol and fluvoxamine[22].

Activity of CYP1A2 can be measured *in vivo* by administration of probe drugs such as caffeine, phenacetin and theophylline[23]. Presently, caffeine is the most commonly used probe because of its low toxicity and good acceptance[24]. Caffeine is primarily metabolized *via* N3-demethylation yielding the eliminated metabolite of paraxanthine (1,7-dimethylxanthine). This reaction accounts for 84 per cent of total caffeine biotransformations and is specifically catalyzed by CYP1A2[18,23]. Paraxanthine/caffeine ratio has been recognized as a good index for CYP 1A2 activity because paraxanthine is a major metabolite and catalyzed only by CYP1A2[25].

The main purpose of this study was to compare CYP 1A2 activity in female subjects that were automobile exhaust exposed and non-automobile exhaust exposed using serum paraxanthine/caffeine ratio as an index. Carbon monoxide level in blood was also determined to ensure that the subjects were exposed to automobile exhaust.

MATERIAL AND METHOD

Subjects

The study was approved by the Ethic Committee of the Faculty of Medicine, Chulalongkorn University. Fifteen exhaust exposed and fourteen non-exposed healthy female volunteers were included in the study after giving informed consent. Age (mean ± SE) of the exposed group was 33.13 ± 1.28 years (range, 25-40 years) and the control (non-exposed) group was 38.71 ± 1.31 (range, 29-45 years). Each subject was in good health confirmed by the clinical laboratory parameters including liver and renal function test. They did not take any drugs or compounds which would interfere with caffeine metabolism such as omeprazole, cimetidine, contraceptives, cigarette smoking and alcohol. They were not pregnant and had no history of liver or renal disease. All subjects abstained from taking caffeine containing food and beverages for at least three days before experimentation. The study group exposed to automobile exhaust for at least one year while the control group was not exposed. Each subject took a 180 mg single oral dose of caffeine solution and blood samples were collected before and five hours after caffeine intake which is the optimum time for paraxanthine detection[26]. Serum samples were separated by centrifugation and stored at -20°C until analysis.

Chemicals

Caffeine (anhydrous, BP grade, batch no 71015), paraxanthine and 8-chlorotheophylline as the internal standard were obtained from Sigma Chemical Co. Ltd. Acetic acid and trichloroacetic acid were purchased from MERK. Methyl alcohol HPLC grade from Lab Guard. Acetonitrile HPLC grade from Scharlau Chemie S.A. Tetrahydrofuran was obtained from Farmitalia Carloerba. Double distilled water was used throughtout this investigation.

Apparatus

HPLC from Spectra System Thermo Separation Products consisted of a model P1000 for delivering the mobile phase, a model automatic injector AS3000 for sample injection and UV detector with a

model of UV1000 used to monitor caffeine, 8-chlorotheophylline and paraxanthine at wavelength of 273 nm. A μ-bondapak C18 stainless steel column (30 cm, 3.9 mm, I.D. Water Associates) was suitable in the condition. A computer system with PC1000 software was used to analyse peak and set the standard system. CO level in blood was determined by spectrophotometer.

Sample preparation

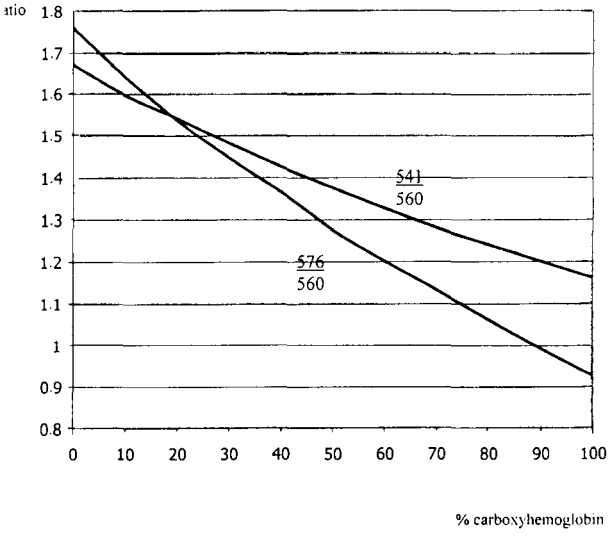
The sample separation was modified from Koch JP et al[25]. Serum protein precipitation was archived using the following method, 500 μl of serum was added with 200 μl of internal standard, 500 μl of methanol and 500 μl of 10 per cent trichloroacetic acid. All were mixed on a vertex for 1 minute and centrifuged at 4,000 rpm for 15 minute. 50 μl of the supernatant was injected into the HPLC system.

Chromatographic condition

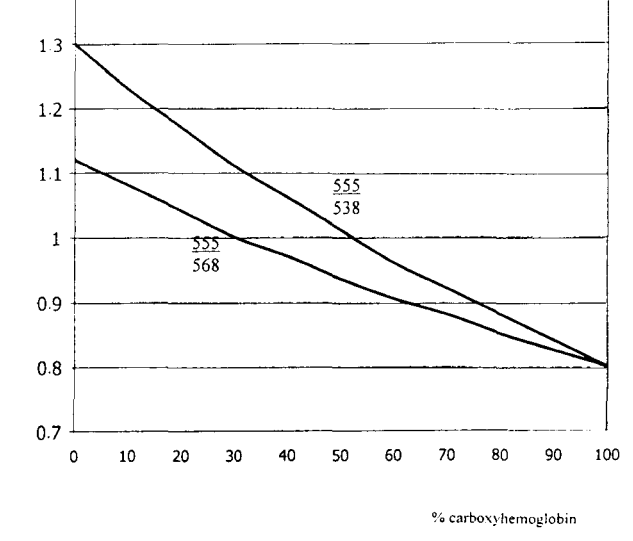
The mobile phase for paraxanthine and caffeine assay was the mixture of acetic acid, tetrahydrofuran, acetonitrile and water (1:3:40:456) with the pH adjusted to 5.6. The mobile phase was delivered to HPLC system at flow rate of 1.2 ml/min. Quantitation was based on integration of peak areas by program computer software.

Blood carbon monoxide determination

Blood carbon monoxide was determined according to the method of Flanagan RJ et al[27]. Briefly, 250 ml of double distill water was shaken for five minutes followed by an addition of 1 ml of 25 per cent ammonium hydroxide solution. One hundred millitre of the solution was then added with 1 ml of blood and centrifuged for five minutes. The supernatant was measured spectrophotometrically at 541, 560 and 576 nm. The old sample cuvette was added with a few grains of sodium dithionite, gently mixed and was then measured at 538, 555 and 568 nm. The ratios of 541/560, 576/560, 555/538 and 555/568 were used to calculate per cent carboxyhemoglobin in blood samples *via* comparing of the standard curve, Fig. 1.



Graph 1



Graph 2

Fig. 1. Standard curve for carbon monoxide assay, the ratios of 541/560, 576/560 are compared in graph 1 and the ratios 555/538, 555/568 are compared in graph 2.

Table 1. Demographic data of the control and study group.

Parameter	Normal value	Control (n=14)		Exposed (n=15)	
		Range	Mean ± SE	Range	Mean ± SE
Age (yrs)	-	29-45	38.71 ± 1.31	25-40	33.13 ± 1.28
Weight (kgs)	-	45-74	59.86 ± 2.34	42-75	54.27 ± 2.09
Height (cm)	-	150-168	158.79 ± 1.11	141-165	155.8 ± 1.44
SBP (mmHg)	90-140	100-130	115 ± 2.03	90-120	106.67 ± 2.52
DBP (mmHg)	60-90	60-90	74.29 ± 2.27	60-80	68.67 ± 1.91
AST (U/L)	0-38	14-30	19.71 ± 1.05	14-30	18.4 ± 1.1
ALT (U/L)	0-38	8-32	17.14 ± 1.66	8-34	15 ± 1.59
TB (mg/dl)	0-1	0.21-0.62	0.37 ± 0.03	0.29-0.79	0.47 ± 0.03
Albumin (U/L)	3.4-5.5	3.5-4.4	3.93 ± 0.06	3.7-4.6	4.23 ± 0.05
AP (U/L)	39-117	29-93	59.79 ± 4.54	44-117	68.47 ± 5.13
BUN (mg/dl)	10-20	7-16	10.36 ± 0.6	7-16	10 ± 0.67
Creatinine (mg/dl)	0.5-2	0.7-1	0.86 ± 0.02	0.4-1	0.76 ± 0.04

Note : SBP = systolic blood pressure, DBP = diastolic blood pressure, AST = aspartate aminotransferase, ALT = alanine aminotransferase, TB = total billirubin, AP = alkaline phosphatase, BUN = blood urea nitrogen

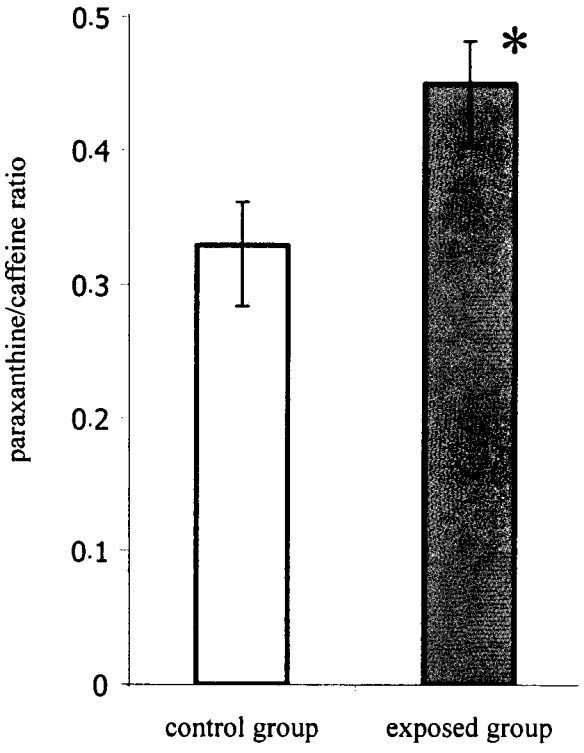


Fig. 2. Serum paraxanthine/caffeine ratio of the exposed and non-exposed groups 5 hours after oral administration of 180 mg of caffeine. The figure shows mean ± SE of n = 14 in the control group and n = 15 in the exposed group.

*** denotes significant differences ($p < 0.05$) between the control and the exposed group.**

Data analysis

Differences of serum paraxanthine/caffeine ratios and CO levels between the control group and exposed group were determined by Student's *t*-test in SPSS Program at p-value of 0.05.

RESULTS

Subjects used in the control and study groups were in the similar ranges of age, weight and height. In addition, the health status of both groups was comparable as indicated by the non-significant differences of all basic clinical laboratory parameters that were all in the normal limit range (Table 1).

Five hours after oral administration of 180 mg caffeine to each subject of both the control and study groups, serum samples of all subjects were measured for paraxanthine and caffeine concentrations. The results showed paraxanthine/caffeine ratio of the exposed group was signifiicantly higher than that of the non-exposed group with the mean ± SE of 0.45 ± 0.05 and 0.33 ± 0.03, respectively; $p < 0.05$ (Fig. 2).

To confirm that the subjects were exposed to automobile exhaust, blood CO were also determined in all subjects The results showed that the blood CO level in exposed subjects was significantly higher than the non-exposed subjects (mean ± SE of % carboxyhemoglobin were 4.03 ± 0.21 and 3.01 ± 0.18, respectively) (Fig. 3).

Disscussion and conclusion

Several methods can be used to determine the activity of CYP1A2. Those methods included caffeine breath test, urinary caffeine metabolites ratio and plasma or serum caffeine metabolites ratio[23]. In the present study, the authors used serum paraxanthine/caffeine ratio as an index of CYP1A2 activity because paraxanthine is a major metabolite of caffeine and this metabolic pathway is catalyzed solely *via* CYP1A2[23,25]. In addition, caffeine breath test

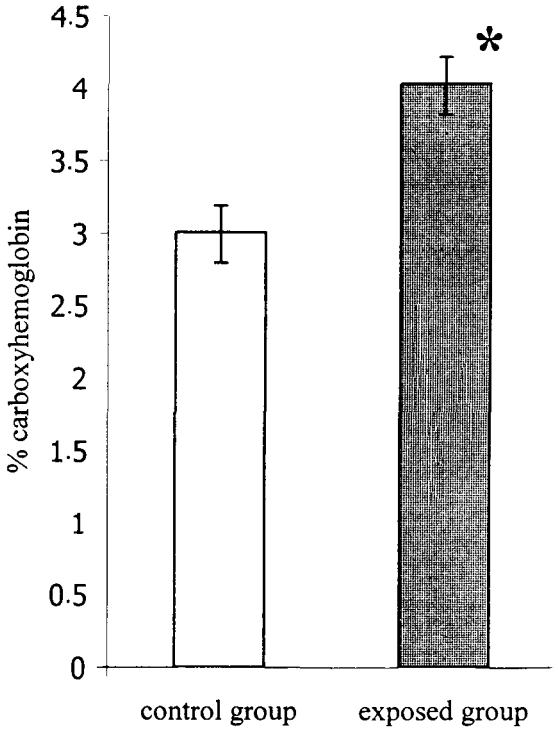


Fig. 3. Blood CO level of the exposed and non-exposed groups. The figure shows mean ± SE of n = 14 in the control and n = 15 in the exposed groups.

*** denotes significant differences ($p < 0.05$) between the control and the exposed group.**

necessarily requires isotope labeled and specialized equipment for measuring the labeled carbon dioxide in exhaled air[23]. Urinary caffeine metabolite ratio which is based on either secondary and tertiary metabolites, are not ideal indices of CYP1A2 activity because these metabolites are not formed exclusively by CYP1A2[28]. Furthermore, this method might vary substantially from several factors such as urinary flow, interethnic differences in renal function and sampling time of urine collection[23,24]. Since the method of determining serum paraxanthine/caffeine ratio is simple and reliable, this ratio is probably an optimum method for determining human CYP1A2 activity[25].

The dosage of 180 mg of caffeine used in this study is an approximate amount of caffeine contained in one cup of coffee. Besides causing no adverse effects, this dosage is suitable for monitoring serum paraxanthine and caffeine[26]. The half life of caffeine was about 3 to 7 hours and cleared from the body within 12 to 28 hours[29]. The pilot study showed that the optimum time for sample collection with the highest paraxanthine level was found to be five hours after caffeine administration[26]. The studies of Carillo JA[30] and Ou-Yung DS[24] chose the times of four and six hours after caffeine intake for sample collections, respectively. Female subjects were used in both the control and exposed group because male populations usually smoke cigarettes and drink alcohol, the factors influence CYP activity. All other disease factors that might affect hepatic drug metabolizing enzymes were checked by determining various clinical chemistry parameters. Age and weight were also comparable between the control and the exposed groups.

The results from this study showed that serum paraxanthine/caffeine ratio of the exposed group was significantly higher than that of the non-exposed group. It implied that CYP1A2 was induced in the automobile exhaust exposed subjects. Due to the difficulty of PAHs determination, indirectly determine the level of blood CO, the incomplete combustion produce of carbon-containing materials also normally found in automobile exhaust. The results showed that blood CO level of the exposed group was significantly higher than that of the control group. This ensured that the exposed group was significantly more exposed to automobile exhaust than the control group. Thus, the induction of CYP1A2 found in the exposed group was possibly caused by the constituent in the exhaust, mainly the PAHs.

In conclusion, serum paraxanthine/caffeine ratio was significantly higher in the automobile exhaust exposed group than in the non-exposed group. This ratio is an index for CYP1A2 activity which is generally modulated by many xenobiotics such as PAHs. Thus, the ratio could be used to determine PAHs exposure. From this result, the exposed group has a higher risk to chemical carcinogenesis.

ACKNOWLEDGEMENT

This investigation was supported by the Rachadapiseksompoj China Medical Board Reseach Fund and Ministry of University Affairs (MUA)-CU Thesis Grant.

(Received for publication on April 6, 2003)

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อัตราส่วนของพาราแซนธีน/แคฟเฟอีน : ดัชนีวัดการทำงานของเอนไซม์ไซโตโครม พี450 1เอ2 ในกลุ่มคนที่ได้รับสารโพลีไซคลิคอะโรมาติคไฮโดรคาร์บอน

สุพีชา วิทยเลิศปัญญา, วทม,*
เยาวรัตน์ หินซุย, วทม, สมทรง ลาวัณย์ประเสริฐ, วทด***

โพลีไซคลิคอะโรมาติคไฮโดรคาร์บอน (พีเอเอ็ช) เป็นสารที่พบทั่วไปในสิ่งแวดล้อม เกิดจากกระบวนการเผาไหม้ไม่สมบูรณ์ของสารประกอบอินทรีย์ สารเหล่านี้เมื่อถูกเปลี่ยนแปลงจะได้เมแทบอไลต์ที่มีฤทธิ์ซึ่งเมื่อจับกับ DNA มีผลก่อมะเร็ง เป็นที่ทราบกันดีว่าพีเอเอ็ชเป็นสารเหนี่ยวนำการทำงานของเอนไซม์ไซโตโครม พี450 เช่น CYP1A1 และ CYP1A2 แคฟเฟอีนถูกเปลี่ยนแปลงโดยเอนไซม์ CYP1A2 ได้เมแทบอไต์เป็นพาราแซนธีน ดังนั้นจึงนิยมใช้แคฟเฟอีนเป็นสารในการศึกษาการทำงานของเอนไซม์นี้ การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบการทำงานของเอนไซม์ CYP1A2 ในเพศหญิงที่ได้รับควันและไม่ได้รับควันจากท่อไอเสียรถยนต์โดยใช้อัตราส่วนของพาราแซนธีน/แคฟเฟอีนเป็นดัชนีวัดการทำงานของเอนไซม์ ให้กลุ่มตัวอย่างแต่ละคนรับประทานแคฟเฟอีนขนาด 180 มิลลิกรัม 1 ครั้ง เจาะเลือดก่อนและหลังรับประทานแคฟเฟอีน 5 ชั่วโมง วิเคราะห์หาความเข้มข้นของพาราแซนธีนและแคฟเฟอีนในซีรั่มโดยวิธี HPLC วัดระดับคาร์บอนมอนอกไซด์ในเลือดโดยใช้เครื่องสเปกโทรโฟโตมิเตอร์ พบว่าอัตราส่วนของพาราแซนธีน/แคฟเฟอีนในซีรั่มในกลุ่มที่ได้รับควันจากท่อไอเสียรถยนต์มีค่าสูงกว่ากลุ่มที่ไม่ได้รับควัน โดยมีค่าเฉลี่ยอัตราส่วนของพาราแซนธีน/แคฟเฟอีนเป็น 0.45 $\pm$ 0.05 และ 0.33 $\pm$ 0.03 ตามลำดับ, ($p < 0.05$) คาร์บอนมอนอกไซด์ในเลือดในกลุ่มที่ได้รับควันจากท่อไอเสียรถยนต์มีค่าสูงกว่ากลุ่มที่ไม่ได้รับควัน โดยมีค่าเฉลี่ยของระดับคาร์บอนมอนอกไซด์ในเลือดเป็น 4.03 $\pm$ 0.21 และ 3.0 1$\pm$ 0.18 ตามลำดับ, ($p < 0.05$) การศึกษานี้แสดงให้เห็นว่าอัตราส่วนของพาราแซนธีน/แคฟเฟอีนสามารถใช้วัดการทำงานของเอนไซม์ CYP1A2 ในกลุ่มคนที่ได้รับ PAHs กลุ่มที่ได้รับควันจากท่อไอเสียรถยนต์มีการทำงานของเอนไซม์ CYP1A2 สูงกว่ากลุ่มที่ไม่ได้รับควันและกลุ่มดังกล่าวมีความเสี่ยงต่อการเกิดมะเร็ง

คำสำคัญ : อัตราส่วนของพาราแซนธีน/แคฟเฟอีน, ไซโตโครม พี450 1เอ2, พีเอเอ็ช

สุพีชา วิทยเลิศปัญญา, เยาวรัตน์ หินซุย, สมทรง ลาวัณย์ประเสริฐ
จดหมายเหตุทางแพทย์ ฯ 2546; 86 (ฉบับพิเศษ 2): S310–S317

* ภาควิชาเภสัชวิทยา, คณะแพทยศาสตร์,
** ภาควิชาเภสัชวิทยา, คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330