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Cytochrome P450 enzyme : its clinical role in drug interactions

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Cytochromes P450 constitute a superfamily of hemoproteins that catalyze the metabolism of endobiotics and xenobiotics in human. Their metabolic activities affected by genetic and environmental influences including drugs have been continuously studied both in vivo (probe drug) and in vitro. Hepatic CYP1, CYP2 and CYP3 families are mainly responsible for biotransformation of many drugs. They do also play important role in modulating the toxicity and carcinogenicity of chemicals. Many factors can modify P450 activities such as age, race, nutrients, ethanol and chemicals. There are also wide interindividual variabilities in P450's expression and activity. Individual metabolic capacity of these enzymes can be estimated either by phenotyping or by genotyping approach. Different types of interactions between various groups of drugs due to hepatic enzymes are mentioned : antifungal agents, psychoactive drugs and systemic drugs prescribed by dermatologists. Actually, most drugs cause toxic reaction only rarely without dose-related pattern; genetic enzyme variants; or poor metabolizer of P450 can affect drug metabolism and side-effects. The identification and assay of individual

Objective

1. To introduce the plysicians about cytochrome P450 enyzme.
2. To explain its clinical role in drug intractions.

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P450 enzyme are relevant in clinical settings, from the perspective of drug toxicity and therapeutic effectiveness. Moreover, CYP polymorphism are associated with the risk of onset of various illnesses, including cancers.

Key words : *Cytochrome P450, Biotransformation, Phenotype, Genotype, Poor metabolizer, Drug interaction.*

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ไพลิน อุชชิน, สร้อยสังวาลย์ สาตรักษ์. ไซโตโครม พี 450 : บทบาททางคลินิกเกี่ยวกับปฏิกริยาระหว่างยา. จุฬาลงกรณ์เวชสาร 2545 ม.ค; 46(1): 73 - 84

ไซโตโครม พี 450 เป็นกลุ่มของเอนไซม์ที่มีฮีมเป็นองค์ประกอบ ทำหน้าที่เร่งปฏิกริยาการเปลี่ยนแปลงของสารเคมีหลายอย่างภายในร่างกาย รวมทั้งสารที่ได้รับจากภายนอกร่างกายด้วย ยังคงมีการศึกษาเอนไซม์กลุ่มนี้อย่างต่อเนื่องถึงลักษณะทางพันธุกรรมและสิ่งแวดล้อมต่าง ๆ รวมทั้งยาที่มีอิทธิพลต่อการเร่งปฏิกริยาในร่างกาย เอนไซม์กลุ่มที่ 1, 2 และ 3 ในตับมีบทบาทสำคัญต่อการเปลี่ยนแปลงยาในร่างกาย เอนไซม์นี้ยังมีบทบาทสำคัญในการปรับเปลี่ยนสารเคมีต่าง ๆ ในทางที่จะเกิดพิษหรือก่อเกิดมะเร็ง ปัจจัยที่มีผลต่อการทำงานของเอนไซม์นี้ได้แก่ อายุ เชื้อชาติ อาหาร สุรา และสารเคมีต่าง ๆ ระดับของเอนไซม์ในแต่ละคนแตกต่างกันได้มาก การประเมินเอนไซม์นี้เป็นไปได้ทั้งจากลักษณะทางกายภาพที่แสดงออกหรือส่วนประกอบทางพันธุกรรม การใช้ยาหลายชนิดร่วมกันอาจเกิดปฏิกริยาระหว่างยา ซึ่งเอนไซม์นี้มีส่วนร่วมด้วย แสดงตัวอย่างในยาต้านเชื้อรา ยาทางจิตเวช และยาทางโรคผิวหนัง ถ้าเอนไซม์นี้มีการกลายพันธ์ที่หน่วยพันธุกรรมอันมีผลให้บกพร่องต่อการเร่งปฏิกริยา พบว่ามีผลต่อการเปลี่ยนแปลงยาในร่างกายและอาจทำให้เกิดผลข้างเคียงของยาด้วย การแยกแยะและตรวจวัดระดับเอนไซม์ช่วยอธิบายถึงกลไกการเกิดการแพ้ยาอันนำสู่การใช้ยาที่มีประสิทธิภาพขึ้น เอนไซม์นี้ยังมีบทบาทสำคัญในการปรับเปลี่ยนสารเคมีต่าง ๆ ซึ่งนำสู่การเกิดโรคต่าง ๆ รวมทั้งมะเร็ง

คำสำคัญ :*ไซโตโครม พี450, การเปลี่ยนแปลงของสารเคมีในร่างกาย, ลักษณะที่แสดงออกทางกายภาพ ลักษณะที่แสดงออกทางพันธุกรรม, พวกที่บกพร่องทางการเร่งปฏิกริยา,ปฏิกริยาระหว่างยา*

Cytochrome P450 (P450) enzymes are heme-containing monooxygenases that play central roles in oxidative, peroxidative and reductive reactions of numerous endobiotics (such as steroids, fatty acids, prostaglandins, biogenic amines and vitamins), and xenobiotics (such as drugs, environmental chemicals, pollutants and natural plant products). Although the enzymes are keys to the activation and detoxification of substances, toxicological and pharmacological in origins, some metabolic processes of foreign chemicals can frequently produce toxic metabolites, some of which are implicated as responsible agents for birth defects and other forms of toxicity, as well as tumor initiation and progression. CYP is the recommended nomenclature for a P450 gene and its corresponding gene products (mRNA, cDNA and enzyme). The primary sequences of more than 400 P450 enzymes are now known together, with their general characteristics and functions. Each P450 gene usually produces a single protein. Because P450 enzymes are the most important xenobiotic metabolizing enzymes, they are also known as drug-metabolizing enzymes.[1] Xenobiotic-metabolizing P450 enzymes are primarily expressed in the liver, as well as in the gastrointestinal tract, kidneys, lungs and epithelial tissues. The unique properties of P450 enzymes, accountable metabolizing thousands of different xenobiotics, are that each P450 can metabolize chemicals of different structures, and two or more P450 enzymes can sometimes metabolize the same compound, albeit at different rates.[2] Drug metabolism and regulation of the P450 expression were often quite different in humans *vis-a-vis* experimental animals.[3] Potential human metabolism, affected by the important genetic and environmental influences including drug interaction, has been continuously studied *in vitro* in human liver microsome for effective prescription and drug development.[4] The majority of toxic and carcinogenic chemicals do not produce detrimental biological effects by themselves, except in acute circumstances. In most cases, activation to electrophiles (radicals that prefer electron) is necessary to produce molecules capable of reacting irreversibly with tissue nucleophiles (radicals that prefer nucleus). Alteration of P450 catalytic activities is important in modulating chemical toxicity and carcinogenicity. Protoxicants and procarcinogens as principal substance forms require bioactivation by individual human P450 enzymes and interindividual variability in the metabolic activities may be key host factors to explain the differences of susceptibility to chemical carcinogenesis among individuals.[5,6] In this review, we summarize and integrate current knowledge about human cytochrome P450 enzymes that may be useful for physicians in clinical practice.

The Human Cytochrome P450 Enzymes

P450 enzymes have been systematically classified, based on their amino acid sequences. After CYP, an Arabic number is inserted to indicate its family which each of them shares at least 40 % of identical amino acid sequence. A capital letter, that follows the family number, identifies its subfamily, each of it member possesses greater than 55 % sequence homology. Individual genes, coding for one specific enzyme, has a second Arabic number after that letter (such as CYP2C9 : its family is 2 and subfamily is C). The enzymes that catalyze the oxidative biotransformation of exogenous compounds, including many drugs are found in the CYP1, CYP2 and CYP3

families. The other families, involved in the metabolism of endogenous substances, are for example, fatty acids, prostaglandins, steroids and thyroid hormones.[1,7] (Table 1)

A few studies show the sex differences in humans, and most of the works suggest that there are no obvious sex-related differences in P450 activities.[10,11] Ages of individuals influences CYP enzyme activity. *In vivo* studies of changes in P450 with age via probe drugs were concluded that the activity is immediately low after birth, and increases to the peaks levels at the young/mature adult and finally decreases in old age (drugs catalyzed by CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A3/4).

Table1. The human CYP1, CYP2 and CYP3 isoenzymes with main representative substrates, inhibitors and inducers. [8,9]

Isoenzyme	Substrate	Inhibitor	Inducer
CYP1A2	Amitriptyline, Clomipramine, Clozapine, Imipramine, Propranolol, R-warfarin, Theophylline, Haloperidol, Verapamil	Flavoxamine Quinolones Erythromycin Ciprofloxacin	Omeprazole Phenobarbital Phenytoin Rifampicin Smoking, Charbroiled meat
CYP2A6	Coumarin, Nicotine	Diethyldithio-carbamate	Barbiturates Dexamethasone
CYP2C9	Tolbutamide, S-warfarin Phenytoin, NSAID	Fluconazole Ketoconazole Metronidazole Itraconazole Sulfaphenazole Ritonavir	Rifampicin Phenobarbital
CYP2C19	Diazepam, Omeprazole, Propranolol, Clomipramine, Imipramine,	Ritonavir Omeprazole	Rifampicin Phenobarbital
CYP2D6	Amitriptyline, Haloperidol, Metoprolol, Timolol, Codeine,	Paroxetine Fluoxetine Cimetidine Fluphenazine Quinidine	Not known
CYP2E1	Acetaminophen, Ethanol	Disulfiram	Ethanol, Isoniazid
CYP3A4	Erythromycin, Cyclosporin, Nifedipine, Midazolam, Testosterone, Cortisol,	Ketoconazole Itraconazole	Rifampicin Barbiturate Phenytoin Dexamethasone Carbamazepine

However in CYP2E1, it is found that activity increases rapidly after birth to reach a level equivalent to that of young/mature adult, then gradually decreases and finally gets faster in old age. [12,13] The systemic hypoxia is shown to alter the function of some CYP enzymes.[14] Cigarette smoke constituents induce several CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1. Many chemical carcinogens are activated by various CYP enzymes to active carcinogens. Induction of the enzymes by cigarette smoking may increase the risk for cancer. Most interaction between cigarette smoking and drugs are in the induction of metabolism.[15] Nutrients, food additives and some conditions (such as obesity and fasting) can modify P450 activities, and consequently influence toxicity. P450 enzymes also influence the toxicity of potential harmful materials found in foods, some natural products and conditions. Non-nutritive dietary chemicals, macronutrients, micronutrients and ethanol influenced the level and activities of P450 enzymes. Changes in pharmacokinetics of benzodiazepines, tricyclic and tetracyclic antidepressants which are mainly metabolized by CYP2C19 and CYP2D6 when ingested together with alcohol, were reported. Ethanol induces acute impairment of the disposition of these drugs, resulting in the impairment of many motor, sensory and neurological functions and possibly sudden death.[16] Nutritional deficiency generally lowers rates of xenobiotic metabolism, except thiamine deficiency and riboflavin deficiency, which enhanced rates of xenobiotic metabolism.[17]

Genetic Polymorphism

Human P450 enzymes show a wide inter-individual variation in their protein expression or catalytic activity, which results in unique drug metabolism phenotypes. The variation can be created by temporary causes, such as enzyme inhibition and induction, or to a permanent genetic mutation or deletion. The specific gene mutations or deletions are sustained within the population, a gene is claimed polymorphic or having multiple forms. Genetic polymorphism has been linked to three classes of phenotypes based on the capacity of drug metabolism. Extensive metabolism (EM) is the characteristic of the normal population. Poor metabolism (PM) subject which develops higher serum drug concentration compared with EM, is an autosomal recessive trait resulted from mutation and (or) deletion of both alleles. Ultraextensive metabolism (UEM) subject, which is an autosomal dominant trait requiring gene amplification, does not obtain therapeutic serum concentration from standard dose treatment. Genetic polymorphism plays a significant role in adverse effect of therapeutic drugs or incidence of exposure-linked cancer. Individual metabolic capacity of enzymes can be estimated by either phenotyping or genotyping approach.

Assessment of Phenotype

Phenotyping is assessed by administrating a probe drug, which is selectively metabolized by the CYP enzyme, followed by measurement of the metabolic ratio (the ratio of drug dosage or unchanged drug to oxidized metabolite in serum or urine). Phenotyping takes into account all internal and external factors that influence the specific enzyme activity, effects of drug-drug interactions and defects in the overall process of drug metabolism. However, the procedures are rather complicated, and difficult

to perform correctly, as well as they may increase the risks of adverse drug reactions.

Assessment of Genotype

Genotyping is to define genetic mutation on the CYP gene that indicates the specific phenotype of drug metabolism. It can be directed by a very simple and fast polymerase chain reaction, followed by restriction fragment length polymorphism techniques (PCR-RFLP) which applied in DNA isolated from leukocytes. It is not affected by an underlying disease or co-administration of drugs. There is a good evidence for some classes of therapeutic agents and environmental/occupational carcinogens that genetic polymorphism of these drug-metabolizing enzymes plays a significant role in adverse effects of therapeutic drugs or incidence of exposure- linked cancer.[4,18,19] Genetic variants of P450 enzymes have been discovered because of their atypical clinical response individuals who have shown abnormal ability to metabolize a drug.

Biotransformation

Metabolism results in detoxification and elimination of xonobiotics including therapeutic drugs or activation prodrug to its biologically active therapeutic or toxin. Most commonly, it changes lipophilic (non polar) compound to hydrophilic (polar) one for excretion system. Drug-metabolizing enzymes are classified as phase I (oxidative) and phase II (conjugative). Through catalysis of oxygenation, oxidation, reduction and hydrolysis reaction, phase I enzymes generate functional groups that may further serve as a site for conjugation to glucuronic acid, sulfate or glutathione, catalyzed by phase II enzymes.[4,20] The catalytic reaction of P450 enzymes conforms to the following stoichiometry.

$$NADPH + H^+ + O_2 + SH \longrightarrow NADP^+ + H_2O + SOH$$

(SH = Sulfhydryl group)

In all mammalian CYP, the reducing cofactor is NADPH. Substrates are steroids, fatty acids, drugs and chemical agents that have an alkane, alkene, aromatic ring or heterocyclic ring. The enzyme binds substrate and oxygen; it accepts two reducing equivalents and two protons; it splits the band between the oxygen atom; it inserts the oxygen atom into the substrate; and it releases the products, water and the oxygenated substrate.[21] (Table 2)

CYP2D6, CYP2C19, CYP2E1, CYP2C9 and several non P450 enzymes, including N-acetyl-transferase, thioprine methyltransferase and dihydropyrimidine dehydrogenase all display polymorplism. From the improved methods of human genetic analysis such as PCR-RFLP and single strand conformational polymorphism (SSCP), more and more gene mutations of P450 enzymes have been identified.Genetic analysis of drug metabolizing enzymes is clinically useful to prevent risk in high drug serum concentration, owing to a genetic deficiency.[22] (Table3).

Table 2. Enzymes involved in drug metabolism in human liver. [21]

Phase I	Phase II
CYP1A2	Glutathione S-transferase
CYP2A6	N-acetyltransferase
CYP2B	UDP-glucuronosyltransferase
CYP2C19	Sulfotransferase
CYP2D6	
CYP2E1	
CYP3A	
NADPH-quinone oxidoreductase	

Table 3. Human polymorphism of drug-metabolizing enzymes.[22]

Enzyme	Allele frequency (%)	
	Caucasians	Orientals*
CYP2C9	EM : 94-98	EM : 80
	PM : 2-6	PM : 20
CYP2C19	EM : 94-98	EM : 80
	PM : 2-6	PM : 20
CYP2D6	EM : 90-97	EM : 99
	DM : 3-10	PM : 0.7

* Mostly studied population were Japanese

Clinical Significance of Cytochrome P450 enzyme in drug interaction

Drug interactions are defined as the possibility that a drug may alter the intensity of pharmacological effects of another drug given concurrently. The alterations can be synergistic, additive or antagonistic. Drug interactions can involve drugs and their environmental chemicals, drugs and nutrients or drugs and diseases. The incidence is as low as 3 % to 5 % in patient staking small numbers of medication, whereas as high as 20 % or more in hospitalized patients. Sometimes without physicians' knowledge, alternative drug use can increase the incidence of drug interaction. It can be classified into three types: pharmacokinetic, pharmacodynamic and pharmacoceutical. Pharmacokinetic interactions refer to interactions that a drug affects the disposition of another by changing its absorption, altering its binding, changing its distribution, transportation, biotransformation and excretion. Pharmacodynamic interactions happen at the site of action through a receptor or physiologic system. Pharmacoceutical interactions arise from physical incompatibilities between drugs. Both pharmacokinetic and pharmacodynamic interactions can involve varieties of P450 isoenzymes. Many of the major pharmacokinetic interactions between drugs are due to hepatic CYP enzymes being affected by previous administration of other drugs.

CYP in Palliative Care

Case reports first serve as a role in alerting physicians to the possibility of a drug interaction. Co-administration, some drugs act as enzyme inducers; whereas others, inhibitors. However, reports of enzyme inhibition are found more often. The incidence of side effects is markedly higher in the elderly and the chronic incurable patients. Physicians understanding the mechanism underlying drug interactions is useful, not only in preventing drug toxicity but also in obtaining more effective therapies for diseases.[9,23-25] In palliative care, some patients suffering from severe pain, pharmacokinetic interactions involve CYP2D6 which catalyzes the conversion of codeine to morphine.[25] Poor metabolizers are at risk for undertreatment if it can not be recognized. Pharmacodynamic interactions with dextromethorphan may cause serotonin syndrome.[25] These findings are significant in pain management which are necessary in this area of medical care.[25]

CYP in Fungal Infection

Most of pharmacokinetic interactions in the systemic azole antifungal drugs are metabolic in origin, and result from the inhibition of CYP-mediated hepatic and/or small intestinal metabolism of coadministrated drugs. All the azoles are inhibitors of CYP3A4.[26]

Ketoconazole is the most potent, followed by itraconazole and then by fluconazole.[26] Ketoconazole and itraconazole are clinically important inhibitors of the clearance of CYP3A substrates such as cyclosporin, tacrolimus, triazolam, midazolam and terfenadine.[26] Coadministration of ketoconazale or itraconazole with cyclosporin or itraconazole with cyclosporin or tacrolimus in organ transplant recipients may be beneficial from the reduction of the cost of immunosuppressive therapy and the risk of fungal infections.[26] Clinically important adverse interaction with specific medications may lead to torsades de pointes, rhabdomyolysis, symptomatic hypotension, excessive sedation, ataxia and ergotism. Torsades de pointes which is a life-theratening vertricular arrhythmia was reported to occur with concomitant administration of the CYP3A4 inhibitors (clarithromycin, diltrazem, erythromycin, itraconazole or ketoconazole) with astemizole, cisapride, pimozide or terfenadine.[27] Severe rhabdomyolysis may precipitate acute renal failure. Rhabdomyolysis happens when lovastatin or simvastatin was coadminstrated with a number of CYP3A4 inhibitors. The susceptibility of midazolam to interactions with CYP3A4 inhibitors is the most problem for patients in the intensive care unit from excessive sedative effect.[27] Ataxia can be avoided for patients requiring long term carbamazepine by physicians' knowledge of CYP3A4 inhibitors.[27] In patients receiving ergotamine, all CYP3A4 inhibitors should be avoided for ergotism's prevention.[27]

CYP in Psychiatry

When two psychoactive drugs that both are substrates for a polymorphic CYP enzyme are administrated concomitantly in psychiatry, each will compete for that enzyme and competitively inhibit the metabolism for the other substrate. This can result in toxicity. CYP2D6 polymorphism has been associated with the risk of various illness, including schizophrenia, Alzheimer's disease, Parkinson's disease, cancer and epilepsy.[13]

CYP in Liver Disease

The pharmacokinetics of many types of drugs metabolized by the liver are modified in patients with hepatic disease. Liver disease can affect the pharmacokinetics by reducing the activity of drug metabolizing enzymes, reducing the plasma synthesis or changing hepatic blood flow. Modifications depend on the characterization of the drug and the severity of the liver disease. Several drugs metabolized by specific CYP isozymes have been used as probe for quantitative tests of liver function and degree of hepatic impairment. Not only pharmacokinetics but also pharmacodynamics are affected by liver diseases. The examples of CYP enzymes which are sensitive to liver disease are CYP1A2, CYP2A6, CYP2C19 and CYP3A.[28]

CYP in Epilepsy

CYP2C9, CYP2C19 and CYP3A4 are mainly isoenzymes for antileptic drugs. Pharmacokinetic interactions between these drugs cause a major complication of epilepsy treatment involving polypharmacy.[29]

CYP in Cardio- vascular Disease

An individual of poor debrisoquine oxidation status (deficiency in CYP2D6) is subject to more intense and prolonged β -blockade due to metoprolol

which produces undesirable side effects such as dizziness, syncope and sinus bradycardia.[30] At least 45 drugs are showed to be oxidized by CYP2D6, including antidepressant, neuroleptics and anti-arrhythmic agents. One should not be surprised that adverse drug interactions might result, particularly in the patients who are treated with simultaneous drugs. Adverse reactions (and even death) have been experienced in individuals who are genetically deficient in CYP2D6 and have used certain drugs.

CYP in Family Planing

Another example is reported on an undesirable event found in the family planing_clinic. Induction of CYP3A4 could lead to enhanced oxidation of the oral contraceptive 17α -ethynylestradiol; and unexpected pregnancies have been experienced in women using rifampicin or barbiturates.[31]

CYP in Drug Abuse

CYP enzymes can activate (such as codeine to morphine) or deactivate (such as nicotine to cotinine) drugs of abuse. In epidemiological studies, they found that CYP2D6 and CYP2A6 null mutation (as phenotypic poor metabolizers) protect individual from becoming codeine and tobacco dependent, respectively.[32] Moreover, individuals with CYP2A6 mutations smoke fewer cigarettes and can quit smoking more easily.[32] Inhibiting CYP2A6 activity also decrease smoking and activation of procarcinogens. The inhibition will alter the kinetics, toxicity, drug reinforcing properties and physical dependence liability of some drugs of abuse and make drugs less pharmacologically attractive.[32]

Conclusion

Cytochrome P450 enzymes are interesting because of their various catalytic reactions which take place all the time through our life. Their activities are influenced by internal factors (i.e. species, genetics, age, sex hormones and diseases) and external factors (i. e. diet and environment).[33] It should be emphasized that only a few drug interactions are clinically significant. They depend on the magnitude of the change of the concentration of the active forms (parent drug and/or metabolites) at the sites of pharmacological actions and the therapeutic index of the drugs. It is necessary for physicians to know the underlying mechanisms of drug inhibition, the metabolic fate of the drug and the enzymes involvement in each metabolic pathway, in order to predict potential drug interactions effectively.[34] Avoidance of unnecessary polypharmacy, selection of alternative agents with lower interaction potential and careful dosage adjustments based on serum drug concentration monitoring and clinical observation, represent the reasonable ways of reducing risks of such interactions. Thus, understanding CYP enzymes, not only in preventing adverse effects from drugs, but also in inventing safer therapies for physicians. By mimicking some P450 gene defects, individuals can decrease the risk of drugs or tobacco dependence. This may be a new trends of treatment in the future.

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง **"ไซโตโครม พี 450: บทบาททางคลินิกเกี่ยวกับปฏิกริยาระหว่างยา"** โดยตอบคำถามข้างล่างนี้ พร้อมกับส่งคำตอบที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม แล้วใส่ซองพร้อมซองเปล่า (ไม่ต้องติดแสตมป์) จ่าหน้าซองถึง ตัวท่าน ส่งถึง

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หน่วยจุฬาลงกรณ์เวชสาร
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จุฬาลงกรณ์เวชสารขอสงวนสิทธิ์ที่จะส่งเฉลยคำตอบพร้อมหนังสือรับรองกิจกรรมการศึกษาต่อเนื่องอย่างเป็นทางการ ดังกล่าวแล้วข้างต้นสำหรับท่านที่เป็นสมาชิกจุฬาลงกรณ์เวชสารเท่านั้น สำหรับท่านที่ยังไม่เป็นสมาชิกแต่ถ้าท่านสมัครเข้าเป็นสมาชิกจุฬาลงกรณ์เวชสารสำหรับวารสารปี 2545 (เพียง 200 บาทต่อปี) ทางจุฬาลงกรณ์เวชสารยินดีดำเนินการส่งเฉลยคำตอบจากการอ่านบทความให้ตั้งแต่ฉบับเดือนมกราคม 2545 จนถึงฉบับเดือนธันวาคม 2545 โดยสามารถส่งคำตอบได้ไม่เกินเดือนมีนาคม 2546 และจะส่งหนังสือรับรองชนิดสรุปเป็นรายปีว่าท่านสมาชิกได้เข้าร่วมกิจกรรมการศึกษาต่อเนื่องที่จัดโดยจุฬาลงกรณ์เวชสาร จำนวนกี่เครดิตในปีที่ผ่านมา โดยจะส่งให้ในเดือนเมษายน 2546

คำถาม - คำตอบ

1. What is the important metal in P450 molecule ?
   a. Zn
   b. Hg
   c. Fe
   d. Mg
   e. Al

✂.....

คำตอบ สำหรับบทความเรื่อง **"ไซโตโครม พี 450: บทบาททางคลินิกเกี่ยวกับปฏิกริยาระหว่างยา"**
จุฬาลงกรณ์เวชสาร ปีที่ 46 ฉบับที่ 1 เดือนมกราคม พ.ศ. 2545
รหัสสื่อการศึกษาต่อเนื่อง 3-15-201-2000/0201-(1002)

ชื่อ - นามสกุลผู้ขอ CME credit ..... เลขที่ใบประกอบวิชาชีพเวชกรรม.....
ที่อยู่.....

1. (a) (b) (c) (d) (e)
2. (a) (b) (c) (d) (e)
3. (a) (b) (c) (d) (e)
4. (a) (b) (c) (d) (e)
5. (a) (b) (c) (d) (e)

2. CYP is recommended for naming P450 gene and its

a. tRNA
b. mRNA
c. cRNA
d. variants
e. allele

3. Cigarette smoke constituents can induce the activity of

a. CYP1A2
b. CYP2C9
c. CYP2B6
d. CYP2D6
e. CYP2C19

4. Which is the enzyme involved in phase I of drug metabolization ?

a. Glutathione S-transferase
b. Sulfotransferase
c. N-acetyltransferase
d. CYP2E1
e. UDP-glucuronosyltransferase

5. These CYP enzymes are sensitive to liver disease, <u>except</u>

a. CYP1A2
b. CYP2A6
c. CYP2C19
d. CYP3A
e. CYP2D6

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านหน้า

ศาสตราจารย์นายแพทย์สุทธิพร จิตต์มิตรภาพ
ประธานคณะกรรมการการศึกษาต่อเนื่อง
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
หน่วยจุฬาลงกรณ์เวชสาร ตึกอบรมวิชาการ ชั้นล่าง
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