

The Cytochrome P450 System: Helping to Teach Its Importance in Drug Metabolism and Drug Interactions

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PROLOGUE

Knowledge of the cytochrome P450 system is important for the pharmacist because this enzyme participates in a number of drug interactions which may affect therapeutic outcomes and cause drug-induced toxicities. To help students understand the types of reactions catalyzed by P450 forms, its regulation, and its role in drug interactions, it has been useful to supplement textbook material with additional information which demonstrates its importance to the pharmacy student. The use of drug advertisements, drug information reports, case presentations, and current news stories provide additional ways for pharmacy students to understand the practical importance of this complex enzyme system.

INTRODUCTION

A tremendous amount of research has been invested in characterizing the cytochrome P450 system, because of its role in steroid hormone formation, carcinogen activation, and drug metabolism. This last topic, metabolism of drugs, has made the P450 enzyme system an important topic in pharmacy and medical school curricula. For many years, discussion of the P450 system to pharmacy students has focused on the different types of reactions which are catalyzed by this enzyme system. Excellent chapters have been published in pharmaceutical and toxicology textbooks which describe the different P450-mediated reactions(1-4). In recent years, the substrate specificities of individual human P450 enzymes have been established(1,2,5). In addition to the basic chemical reactions catalyzed by P450 forms, effects of inhibitors and inducing agents on P450-mediated reactions are important topics for students to understand. It has become increasingly important for pharmacy students to understand the P450 enzyme system because of the number of drug interactions documented to involve this enzyme system(6-8). However, the significance of this enzyme system may not be perceived by first or second year PharmD students who view these proteins as catalyzing different types of hydroxylation reactions. Reading a textbook chapter on P450-mediated drug metabolism reactions or hearing a lecture on this subject may not, by itself, impress upon the students that this enzyme system is an important determinant in the regulation of drug plasma levels and in the development of drug interactions.

Recently, Ruenitz(9) discussed problems of presenting drug metabolism information to pharmacy students, methods of delivering this material, and what had proven to be effective in information transfer. In this evaluation of teaching the principles of drug metabolism(9), students were found to obtain greater satisfaction in a discussion-based

approach in which they read a textbook chapter on drug metabolism and answered specific fact-based questions on the reading material. Misconceptions that were found in the student responses were discussed and clarified and then students were asked to answer more conceptual questions on specific drug metabolism topics(9). This method of instruction is indeed effective in promoting an understanding of the principles of drug metabolism. In addition to assigning a textbook chapter on drug metabolism and discussing this material in a lecture format, I have found that supplementing material about the P450 system that students may routinely encounter as professional pharmacists is also effective in demonstrating the importance of the P450 enzyme system. The topic of drug metabolism is taught at Washington State University as one section of a four-part course on the basic principles of pharmacology to first year PharmD students. This article addresses the use of drug advertisements, drug information reports, case studies, and news reports as additional material to supplement textbook and lecture material to demonstrate the importance of the P450 system in drug metabolism.

DRUG ADVERTISEMENTS

One easily obtainable teaching aid which has proven to be effective in introducing the P450 system to students is the detailed information that accompanies the drug advertisements published in both popular and professional journals. Several advertisements list under the subheading of "Drug Interactions" the specific P450 forms which metabolize drugs and discuss potential drug interactions. In some cases, drug advertisements do not list the specific P450 form involved, but make a general statement that the hepatic P450 system or mixed function oxidase is responsible for its metabolism. The advertisements also show the importance of understanding specific chemical reactions catalyzed by P450 enzymes. For example, the advertisement for Effexor (venlafaxine) describes its conversion to an active pharmacological agent by an O-demethylation reaction and the information sheet on Sporanox (itraconazole) indicates its hydroxylated product also retains its inhibitory effect on a P450 enzyme.

These advertisements also describe the role of enzyme inhibition in drug interactions. For example, the inhibition of P450 2D6 by quinidine is described in the information sheet on Ultram (tramadol). This information may augment lecture material on the inhibition of P450 2D6 to increase student awareness that quinidine inhibits this P450 and may convert extensive metabolizers into poor metabolizers. A common interaction which is widely described in drug advertisements concerns the concurrent usage of substrates

or inhibitors of P450 3A4 with terfenadine or hismanal. These ads can be used to demonstrate the clinical importance of enzyme inhibition. In addition to inhibition of P450 reactions, drug interactions which involve P450 induction are also described in drug advertisements. Warnings that phenytoin and rifampin may alter effects of drugs metabolized by P450 3A4 are commonly described in these drug advertisements. They also emphasize how lifestyle parameters may affect drug therapy. A description of an interaction between smoking and drug levels was found in the advertisement for Nicoderm which describes the "Deinduction of hepatic enzymes on smoking cessation" to explain why dosages of acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, and theophylline may be reduced in an individual who stops smoking. They also focus attention on the possible role of the P450 system in the production of reactive metabolites which may act as teratogens, mutagens or carcinogens. Drug advertisements have been useful for presenting practical information on the P450 system and for monitoring whether students understand how P450 forms are involved in drug interactions.

One practical problem when using drug advertisements is the different designations given to P450 forms. The nomenclature system for the P450 system and the number of P450 forms which exist(10) may present a major stumbling block in understanding this enzyme system. The chapter by Williams(1) gives an excellent description of the current P450 nomenclature system which is now almost universally used in research papers, but which is not used in most drug advertisements or information sheets. Because Roman numerals were initially used to describe P450 forms prior to the adoption of the current system, some advertisements still use Roman numerals to designate specific P450 forms (e.g., P450IID6, P450IIIA4) whereas in most others, the presently accepted Arabic numerals are used (P4502D6, P4503A4). In a few advertisements, subscripts are used to denote the P450 form (e.g., P₄₅₀IIIA₄, P₄₅₀IID₆). In addition, the presently accepted nomenclature uses the preface CYP to designate that the protein is a P450(10) and some advertisements have started to use the CYP nomenclature. However, P450 is still used as the preface in most drug advertisements and in many articles published in clinical journals. Thus students may be confused about the individual protein forms and their designations and an explanation should be given why multiple names have been given to P450 forms.

DRUG INFORMATION REPORTS

In addition to drug advertisements, detailed drug information reports distributed by the pharmaceutical companies are an excellent learning source for students to understand the importance of P450 forms in drug interactions. A few years ago, a group of pharmacy students was given an assignment to write a report on the interaction of terfenadine with other drugs. The emphasis of the assignment was how terfenadine's metabolism by the P450 system was involved in its toxicity, since stories about its cardiovascular effects had recently been reported. One student contacted the manufacturer (Marion Merrell Dow) by phone and received the drug information report which described the specific role of CYP3A4 in its metabolism. The development of cardiac arrhythmias was described for some individuals who received either erythromycin or ketoconazole with terfenadine. This assignment was useful in focusing the

student's attention on basic pharmacokinetic concepts, biochemical principles of enzyme inhibition, substrate specificity of the P450 system, drug interactions, drug-induced toxicity, and why the drug was on the market for such an extended time period before its toxic effects became known. The information obtained from the pharmaceutical company indicated how thorough an understanding of P450 enzymes are necessary to understand certain drug interactions.

CASE PRESENTATIONS

Another useful teaching aid to emphasize the importance of P450 forms is to use case presentations which describe how P450 forms may be involved in drug interactions. Recent articles have been published which present patient case studies of drug interactions that involve induction or inhibition of a P450 form(7,8). These case presentations provide an easy way to emphasize the importance of genetic polymorphisms which involve P450 forms(2,11,12). Research has identified individuals who lack functional P450 forms in the CYP2C19 and CYP2D6 subfamilies(2,11,12). These case examinations are an effective means of informing students how P450 enzymes catalyze reactions that regulate circulating levels of the pharmacologically active form of the drug. For example, the analgesic effect of codeine has been reported to result from the CYP2D6-mediated O-demethylation of about 10 percent of the codeine to form morphine(11). Individuals who lack a functional CYP2D6 will be unable to convert the codeine to morphine and achieve the analgesic effects of this drug. Thus the reaction pathway can be given, the role of CYP2D6 discussed, and information about its polymorphic expression presented in a problem-based fashion. It provides a format to inform students of inter-individual and inter-ethnic variations to a drug treatment. Knowledge that certain polymorphisms may be more prevalent in one ethnic group than another(2,11,12) may focus attention on adverse drug reactions in a certain patient population. Case presentations are useful in informing students that an individual who has had an abnormal response to one drug which is known to be metabolized by a specific P450 form may also be susceptible to abnormal effects of other drugs catalyzed by this same form. Since noninvasive techniques may be available to examine whether an individual is a poor or rapid metabolizer of certain drugs, these tests can be discussed in ascertaining if an individual possesses a genetic polymorphism for a particular P450 form.

In addition to articles which present case studies that were cited earlier(7,8), clinical studies published in various pharmacology and medical journals can also serve as examples of P450's role in drug metabolism and in drug interactions(13-17). For example, in the study by Mirike and Roden(17), quinidine was administered at subtherapeutic levels to individuals to inhibit P450 2D6 activity. This prevented the rapid metabolism of propafenone in extensive metabolizers which allowed the drug to reach therapeutic levels and block the isoproterenol-mediated increase in heart rate. A dose-response curve is presented in this article(17) which describes how P450 2D6 activity affects the action of propafenone and the inhibition of P450 2D6 by quinidine converts extensive metabolizers into poor metabolizers. Caution must be used in selecting research studies from scientific journals, because first or second year

PharmD students may not understand detailed research techniques or the ability to interpret complicated data. The lecturer may have to simplify the data presented in figures and tables before discussing the data with the students.

NEWS REPORTS

Another informational source which may show the importance of the P450 system to students is recent news reports on drug interactions. Two news stories were reported in 1995 which re-inforced the information students received on the P450 system. The first involved how consumption of alcoholic beverages may increase the risk of liver damage in patients taking high, but not excessive levels of acetaminophen. The alcohol story focuses attention on the role of CYP2E1 in the formation of a toxic metabolite from acetaminophen and how alcohol induces this P450 form by protein stabilization(2). The second news event concerned how grapefruit juice may increase the effectiveness of certain drugs such as cyclosporin. This story on grapefruit juice emphasizes how compounds in food such as naringenin can bind to CYP3A4 and act as an enzyme inhibitor(18,19). Since cyclosporin is actively metabolized by intestinal CYP3A forms, absorption of cyclosporin may be increased when taken concurrently with grapefruit juice, because the naringenin acts as an inhibitor to prevent cyclosporin metabolism. The interaction between P4503A4 and absorption of cyclosporin may be discussed. This news story can be used in conjunction with scientific literature(19,20) to emphasize drug-food interactions. These topics have been known in the research arena for several years and are probably discussed already in most lectures on drug metabolism. However, presentation of these stories as current events by discussing a recent newspaper article or newscast video re-emphasizes the information for the students and alerts them that they may be asked questions on these topics by their customers or patients. These stories also provide an effective approach for discussing the importance of P450-mediated reactions to students.

SUMMARY

The use of these additional informational sources have helped students learn the importance of the cytochrome P450 system and how drug metabolism may have a significant role in the development of drug interactions and drug-induced toxicities. They do not replace textbook material on the different chemical reactions catalyzed by the P450 enzymes or how this enzyme is regulated. These materials provide students an appreciation of its practical importance and may help some students understand why it is necessary to learn the details of this system.

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