EPIDEMIOLOGY, OUTCOMES RESEARCH, AND DRUG INTERACTIONS

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SUMMARY

Drug interactions are one of several outcomes (typically adverse) associated with drug therapy. The bulk of the clinical literature that has been published about drug interactions has focused either on the mechanisms, pharmacokinetic studies, or cases observed by clinicians. However, when it comes to the true risk of a drug interaction, or the probability of such an interaction occurring in a given population, a dearth of information is available. This area is opportune for the application of epidemiological and outcomes-based studies.

KEY WORDS

epidemiology, drug interactions, outcomes

INTRODUCTION

A drug interaction occurs when the effects of one drug are changed — either in magnitude or duration — by the prior or concomitant exposure to another drug, food, or a host of environmental exposures, such as organic solvents, heavy metals, or cigarette smoke. If an interaction does occur between a drug and another xenobiotic, one of three outcomes may ensue: (1) drug toxicity, (2) a decreased effect of the drug, sometimes resulting in complete loss of therapeutic efficacy, or (3) an entirely new and unexpected response.

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Although a wealth of studies have been conducted on the mechanisms of drug interactions, or *how* they occur, far less work has been done on *how often* they occur. One study of prescriptions brought by patients to community pharmacies found a 4.1% incidence of drug interactions /1/. In another study, investigators screened more than 2,400 patients over 25,000 days, and found that 5% of patients were taking drugs that could interact /2/. Potential interactions, of course, are a very different matter from clinically significant interactions. Case confirmation is also a limitation with many drug-interaction studies; this is needed to confirm that the outcome is indeed an interaction rather than the subjective conclusion of a health care practitioner. The frequency and risk factors associated with drug interactions involve a discipline known as epidemiology. Epidemiology is an applied science that focuses on the distribution and 'determinants', or risk factors, of disease development in human populations. A basic tenet of epidemiology is that disease does not occur randomly; individuals are not equally likely to develop a particular disease. Certain persons are at relatively high risk because of specific personal characteristics or their environment. In the case of drug interactions, certain individuals are at greater risk of developing an interaction, because of either a genetic predisposition (e.g., cytochrome polymorphisms) or a host of environmental factors (e.g., environmental exposures, such as smoking or dietary patterns, or occupational exposures).

Outcomes research is the synthesis of several disciplines, including epidemiology, health economics, health services research, statistics, and clinical medicine. Due to increasing pressure to contain costs, outcomes research offers a method to compare the outcomes of different medical treatments.

Figure 1 illustrates the recent supplement that outcomes research offers to traditional clinical research.

The majority of the drug-interaction literature is composed of studies that focus on either mechanisms of action or pharmacokinetic studies, in which concrete, measurable serum levels of the drug are measured at certain time points under controlled conditions.

Pharmacokinetic changes describe how the body manages a drug, specifically its absorption, distribution, metabolism, and excretion (ADME). Rates of availability and distribution are also important, including the rate at which a drug gets to its site of action, dissociates

from its receptor, and is eliminated from the body, all contributing to the magnitude and time course of the pharmacologic effect.

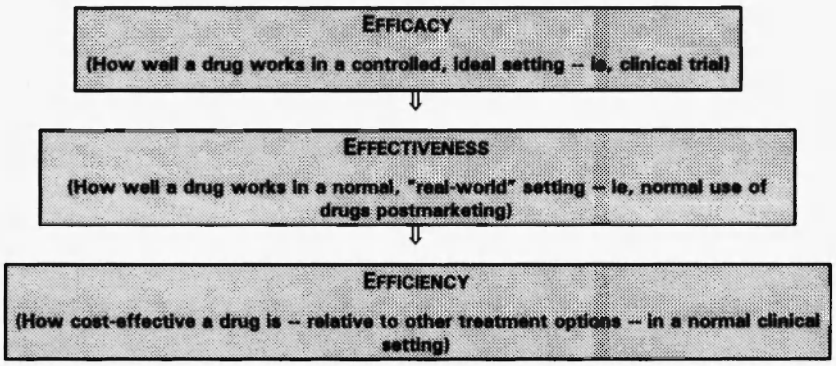

Fig. 1: Movement from traditional clinical research to outcomes-based studies.

Pharmacodynamic drug interactions involve drugs that alter the expected response or actions of other drugs. These interactions may involve drugs directly competing for specific receptors or causing a change in physiologic mechanisms. Examples of pharmacodynamic interactions include drugs binding to certain receptors on nucleic acids or the increased risk of adverse cardiovascular events in women who smoke and take an estrogen-containing oral contraceptive.

CYTOCHROME P-450 ENZYMES AND DRUG METABOLISM

Some of the drugs metabolized by specific cytochrome P-450 enzymes are listed in Table 1. Notice that certain drugs are metabolized by multiple isozymes; this observation has important implications for drug interactions.

TABLE 1

Examples of cytochrome P-450 isozymes responsible for the metabolism of selected drugs

Drug	Isozymes responsible for metabolism
phenacetin	P-4501A2
caffeine	P-4501A2
acetaminophen	P-4501A2, P-4502E1, P-4503A4 (minor pathways; major pathways are Phase II reactions)
theophylline	P-4501A2 (predominately); P-4503A3, 3A4
tolbutamide	P-4502C8, 2C9, 2C10, 2C18
ibuprofen	P-4502C9
omeprazole	P-4502C19, P-4501A2
diazepam	P-4502C19
clozapine	P-4501A2, P-4502D6
coumarin	P-4502D6
codeine	P-4502D6
tricyclic antidepressants	P-4502D6 (primary), 1A2 (secondary pathway)
flecainide	P-4502D6
haloperidol	P-4502D6
timolol	P-4502D6
debrisoquine	P-4502D6
ethanol	P-4502E1, P-4501A2
isoflurane; enflurane	P-4502E1
nifedipine	P-4503A3, 3A4, 3A5
verapamil	P-4503A4
chlorzoxazone	P-4502E1
erythromycin	P-4503A4
astemizole	P-4503A4
corticosteroids	P-4503A4
lovastatin	P-4503A4
lidocaine	P-4503A4
warfarin	
R-warfarin	P-4501A2, P-4503A4
S-warfarin	P-4502C9, P-4503A4
terfenadine	P-4503A4
cyclosporine	P-4503A4

INDUCTION OF THE P-450 ENZYMES

Enzyme induction involves an increase in the biosynthesis of specific enzymes in response to an enzyme-inducing agent /3/. This synthesis of cytochrome P-450 enzymes can be induced by several endogenous and exogenous factors, such as hormones, diet (e.g., certain indole-containing foods), drugs, polyhalogenated chemicals, cigarette smoke, and many other exposures /4-7/. As Table 2 shows, several xenobiotics may induce P-4501A2 and other isozymes. By the end of 1990, more than 150 cytochrome P-450 genes, coding for different proteins catalyzing the oxygenation of a variety of endogenous and exogenous substrates, had been characterized /8/.

As previously discussed, a particular isozyme may be responsible for the metabolism of several substrates; similarly, a particular enzyme inducer may have the capacity to induce several P-450 isozymes (e.g., cigarette smoke, rifampin) (see Table 3). Although one particular xenobiotic may be metabolized by several isozymes, one enzyme typically predominates.

ENVIRONMENTAL EXPOSURES AND DRUG INTERACTIONS

Clinically, it is important to realize that several interactions are actually environmentally driven. That is, drug interactions are not always drug-drug interactions, but may be environmental interactions, associated with a host of environmental or occupational exposures. One environmental exposure, for example, is cigarette smoke, which interacts with several drug products, changing their pharmacokinetics /9/, as shown in Table 4.

From an epidemiologic point of view, it is important to remember that cigarette smokers are a unique cohort; smokers are different from nonsmokers in several ways. These differences may involve economic status, level of education, occupation, physiologic factors, personality, and several other characteristics. Lifestyle habits, personal characteristics, and dietary preferences may confound the enzyme-induction effect of cigarette smoking.

For example, the dietary influence of cruciferous vegetables, which are enzyme inducers, would confound our conclusions regarding the effect of cigarette smoke on drug metabolism if smokers were consistently different from nonsmokers in their consumption patterns.

TABLE 2
Environmental exposures that induce the metabolism of cytochrome P450 enzymes

PESTICIDES
- DDT
- Lindane
- Aldrin
- Kepone®

ORGANIC CHEMICAL COMPOUNDS
- PCBs
- Dioxins

METALS
- Cadmium
- Chromium

DRUGS
- *Anticonvulsants*
  - carbamazepine
  - phenytoin
  - barbiturates
    - phenobarbital
    - pentobarbital
    - secobarbital
    - amobarbital
    - butabarbital
    - heptabarbital
  - primidone
- Rifampin
- Glutethimide (rarely used)
- Ethanol (chronic ingestion)
- Omeprazole

DIET
- Cruciferous vegetables

OTHER ENVIRONMENTAL EXPOSURES
- Cigarette smoke
- Polycyclic aromatic hydrocarbons

TABLE 3
Overlapping specificities of enzyme inducers

Isozyme	Inducer
P-4501A1	Cigarette smoke
P-4501 A2	Cigarette smoke, charcoal-broiled meat, cruciferous vegetables, chronic alcohol ingestion, omeprazole
P-45012C8, 9, 10	Rifampin, barbiturates
P-4502E1	Ethanol, isoniazid
P-4503A4	Rifampin, barbiturates, troleandomycin

If, for example, smokers ingested a diet rich in cruciferous vegetables, the resultant enzyme-induction effect may be largely associated with the smokers' diet rather than the cigarette smoke *per se*. As a result, it is important to assess how smokers' dietary and lifestyle characteristics are different from those of nonsmokers.

Table 5 summarizes some of the dietary and lifestyle differences between smokers and nonsmokers.

In conclusion, the examination of the risk of drug interactions, or the probability of such interactions occurring in a given population, is an opportune area for the application of epidemiological and outcomes-based studies.

TABLE 4

Clinically significant pharmacokinetic interactions between cigarette smoke and drugs

Drug	Mechanism	Effect on cigarette smokers
Theophylline	Induction of the CYP1A2 isozyme	Smoking may lead to reduced theophylline serum levels and decreased clinical effect. The elimination of theophylline is considerably more rapid in smokers than in nonsmokers /10-12/. Because theophylline has a narrow therapeutic-to-toxic ratio (i.e., 5-20 μg/ml), the interaction between it and tobacco smoke is of moderate to high clinical significance.
Tacrine	Induction of the CYP1A2 isozyme	The effectiveness of tacrine in smokers may be decreased. Mean plasma concentration of tacrine is 67% lower in smokers /13/.
Insulin	Decreased insulin absorption, which may be related to peripheral vasoconstriction	Insulin-dependent diabetics who smoke heavily may require a 15-30% higher dose of insulin relative to nonsmokers /14,15/.
Flecainide	Unknown	Based on a meta-analysis, cigarette smoking may reduce flecainide serum concentrations /16/. In one set of studies, patients with premature ventricular contractions required higher flecainide doses than nonsmokers. While the mechanism for this interaction is unknown, an increase in the hepatic metabolism of flecainide has been suggested.
Pentazocine	Unknown	Smoking may cause a decreased pain-relieving effect of pentazocine. As a result, a larger dose of pentazocine may be required in smokers to achieve the same analgesic effect achieved in nonsmokers. One group of investigators found that smokers required 40% more pentazocine than nonsmokers as measured by cumulative urinary pentazocine excretion /17/. This is consistent with another group, who recommend a 50% increase in dose in smokers /18/.

Clozapine	Induction of the CYP1A2 isozyme	The effectiveness of clozapine in smokers may be decreased /19,20/.
Propoxyphene	Unknown	Cigarette smokers - especially heavy smokers (more than 20 cigarettes a day) - may require a higher dose of propoxyphene to achieve the same pain-relieving effect attained in nonsmokers /21,22/.
Propranolol	Increased release of catecholamines (such as epinephrine) in smokers	Smokers taking propranolol may have increased blood pressure and heart rate relative to nonsmokers /23-28/. Smoking may interfere with the efficacy of propranolol in the treatment of angina pectoris.
Tricyclic anti-depressants	Increased hepatic metabolism	Lower drug plasma concentrations of various tricyclic antidepressants (i.e., amitriptyline, desipramine, imipramine, and nortriptyline) have been observed in smokers/29,30/. However, the results of multiple studies are equivocal.
Heparin	Unknown	Smokers may require a higher dose of heparin relative to nonsmokers. One group of investigators found that smokers had shorter heparin half-lives and more rapid heparin elimination compared with nonsmokers /31/.
Chlorpromazine	Unknown	Male smokers may require a larger dose (up to twice) relative to nonsmokers /32/.
Diazepam; Chlordiazepoxide	Unknown, whether pharmacokinetics is altered or end-organ responsiveness is decreased is unclear.	Smokers may require larger doses of diazepam and chlordiazepoxide to achieve sedative effects equivalent to those obtained in nonsmokers /21,22/.

TABLE 5

Significant dietary and lifestyle differences between smokers and nonsmokers

DIETARY DIFFERENCES

Compared with nonsmokers, smokers consume *more*:*

- Coffee
- Alcohol
- Meat - several studies report increased frequency of salami, lunch meat, and canned meat consumption /33,34/
- Cholesterol

Compared with nonsmokers, smokers consume *less*:*

- Fruits
- Vegetables
- Dietary fiber
- Vitamin C
- Thiamin
- Vitamin and/or mineral supplements

LIFESTYLE DIFFERENCES

Compared with nonsmokers, smokers are *less* likely to:

- Exercise actively
- Participate in cancer screening
- Sleep 8 hours per night (i.e., smokers, on average, get less sleep compared with nonsmokers)
- Have meal regularity
- Snack daily
- Eat breakfast (i.e., smokers skip breakfast more often)

*After using regression analysis to control for physical activity, health status, and demographic characteristics.

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