Dose-response relationships in clinical pharmacology
L Lasagna, S Erill, C A Naranjo, editors

AN EPIDEMIOLOGICAL APPROACH TO DOSE-RESPONSE RELATIONSHIPS

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INTRODUCTION

The objective of epidemiology is to provide evidence with regard to the frequency and distribution of diseases in human populations (1,2).

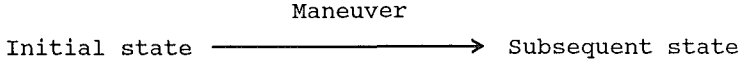
Common research strategies used in epidemiology include those which count the frequency of a disease in a population (such as cross-sectional or longitudinal studies) and those which compare the frequency of disease in one population or group with that in another, including:

a. Prospective experimental case comparison studies of disease etiology or of the effectiveness of treatment (CONTROLLED CLINICAL TRIALS)

b. Prospective observational case comparison studies. (COHORT STUDIES)

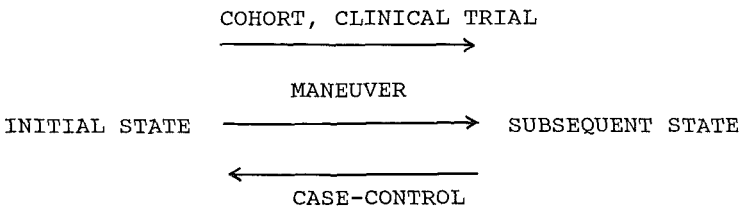
c. Retrospective observational case comparison studies. (CASE-CONTROL STUDIES)

The sequential events of an epidemiological experiment have been conceptualized by Feinstein in 1970 (3) as follows:



Cross-sectional and longitudinal studies are performed in epidemiology to describe or count a disease in a population (e.g. the prevalence of migraine) at one or two given points in time. In contrast, when comparing groups, epidemiological

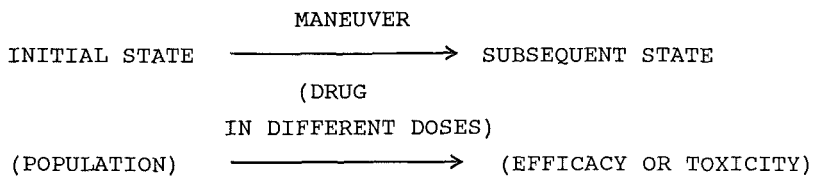
strategies can be summarized as follows:



This paper will deal specifically with one aspect of the maneuver and with its capacity to affect the target state. We will discuss the effect that the potency or intensity (dose) of a given maneuver (i.e. drug) has on the subsequent state (i.e. effect) (whether desired or undesired). For example, if we wish to test that cigarette smoking causes lung cancer, we will explore the effect of smoking different quantities of cigarettes on the rate of appearance of lung cancer in a population.

Because this assessment can be viewed as addressing a larger question, that of CAUSATION, it can benefit from what has been learned on that question in other fields.

We can summarize the particular case we will be analyzing, as follows:

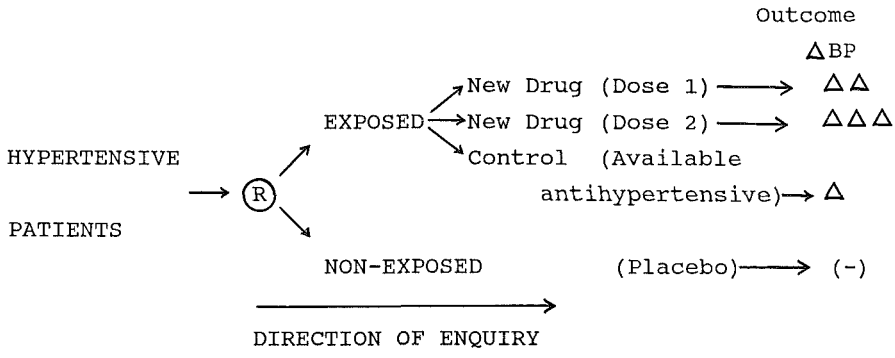


EPIDEMIOLOGICAL STUDIES ASSESSING DOSE-RESPONSE RELATIONSHIP AND EFFICACY

Assessment of the relationship between the dose of drug and its efficacy is rarely found in large epidemiological studies (e.g. case-control or cohort studies). Most of the studies to measure the efficacy of different drug doses on a certain disease state are performed in randomized clinical trials. The reason for this is understandable: Suppose we want to test whether a new diuretic would lower blood pressure in hypertensive patients in a dose-related manner. Most of us would probably start by trying to prove it with a true

experiment in humans in which the hypertensive population would have been randomly allocated to take the new drug or to take the other available anti-hypertensive drugs and then follow them up to see how the different doses of the new drug would affect blood pressure compared to the available antihypertensive.

The basic architecture of the experiment would be as follows:



We will do it this way because the results coming from such an experiment provide the STRONGEST, most RAPID and ACCURATE evidence we can ever obtain about causation. As it happens, this is the way it is almost always done to test the efficacy of a new compound.

However, the clinical goals of anti-hypertensive therapy may be immediate, short-term and long-term. Although the pharmacological and short-term therapeutic aims of anti-hpertensive therapy are to lower blood pressure, the long range goal is to reduce or prevent strokes, myocardial infarction or other vascular complications. Evaluating the literature, it is common to observe that once efficacy and the effect of the dose is evaluated in a controlled clinical trial, evidence of pharmacological efficacy of different doses is generally omitted in Phase 4 and larger epidemiological studies.

Although recent studies have been more strict in providing a better evaluation of long-term outcomes of drug efficacy, (4,5) exploration of the dose-response relationship in such studies is still lacking (4) or looked at in the context of toxicity (side effects) (5).

There are, however, a few examples of COHORT-STUDIES assessing the effect of the dose of a drug on its efficacy. We

are specifically referring to patient-oriented cohort studies such as those coming from intensive drug surveillance programs, namely the Boston Collaborative Surveillance Program (BCDSP) and the University of Chile Drug Surveillance Program (6,7).

The methodologies of these two programs have been extensively described; therefore only relevant aspects will be included here. Nurse or pharmacist monitors are stationed in medical wards in a number of hospitals, where they collect systematic information on consecutively admitted patients. The information includes the usual descriptive characteristics of each patient, together with the diagnoses and details of all drug administrations. When a treatment is begun, the monitor interviews the attending physician to determine the indication, and when a drug is stopped, he/she asks whether or not an adverse reaction occurred. An adverse reaction is defined as any unwanted or unintended effect of a drug (6).

Although the assessment of "efficacy" of the drug is rather crude in this type of cohort studies (i.e. the response is graded as effective, non-effective), Greenblatt and coworkers have shown that in 2542 patients receiving flurazepam for the treatment of insomnia, the clinical efficacy of flurazepam, as judged by the attending physician, depended on the size of the dose. Flurazepam was considered to have unsatisfactory efficacy in 14.3% of patients receiving 15mg but only in 8.6% of those receiving 30mg (8).

In another study, performed at the University of Chile Drug Surveillance Program, assessing the efficacy of furosemide, patients receiving longer treatment with the drug had a significantly better diuretic response than those with a shorter treatment course. Mean duration of treatment in patients with response to furosemide considered "efficacious" was 13 $\pm$ 0.46 days, while for those without such response it was 10.4 $\pm$ 0.9 days, ($p < 0.05$) (9). Since longer duration of treatment determines a larger cumulative dose, this is another example of the influence of the dose on the efficacy of treatment by epidemiological methods.

As discussed above, whereas it is relatively easy to establish the benefit (efficacy) of a certain treatment in a study limited to one or two drugs in different doses, (controlled clinical trial), the methodologies to achieve such a

goal in large epidemiological studies are far from satisfactory. This is probably because the definition of "benefit" (efficacy) in epidemiological terms has not been clearly established. Since "complete cure" (which would be an unambiguous efficacy end-point) is often not achieved, operational definitions of "definite improvement", "prevention of complications" or "reduction of pain" have to be developed before better epidemiological studies in the area of drug efficacy can be performed. Unfortunately, most efforts in analyzing drug effects in epidemiological studies point in the direction of getting more precise information about the risk rather than the benefit, although the latter is the more important aspect (10).

EPIDEMIOLOGICAL STUDIES ASSESSING DOSE-RESPONSE RELATIONSHIP AND TOXICITY

In contrast to the assessment of the relationship of dose and efficacy, which is almost always done in the context of clinical trials, it is much more common to use epidemiological methods to assess the toxicity of drugs.

This is not surprising since the number of patients required to demonstrate that a given adverse event is occurring more frequently in one of the treated groups than in the other is much larger than in the case of efficacy. For example, to be 95% confident of observing one (or more) adverse reactions to a drug we would need to follow three times the reciprocal of the true adverse reaction rate (11). Thus, if the true rate of an ADR is 1/1000, roughly 3000 treated patients would have to be followed to be 95% confident of finding at least one such reaction. Since some of the most severe consequences of drug use such as adverse drug reactions (ADR), behavioural toxicity, drug abuse or drug dependence usually occur at a much lower rate, no randomized trial would be large enough to detect such problems.

Thus, epidemiological approaches are frequently used, including cohort studies and case-control studies.

Using these two methodologies, a clear dose-response relationship for different types of drug toxicity has been established. In the following paragraphs we will illustrate examples of the effects of dose on adverse drug reactions,

direct toxicity such as organ damage, drug abuse and dependence and behavioural toxicity to drugs.

Adverse drug reactions. Adverse drug reactions (ADR) have been defined by the World Health Orgainization as "any response to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy" (12). Estimates hold that between 1 to 3% of patients are hospitalized as a direct result of medications prescribed by physicians or those purchased over-the-counter (13,14). Estimates of morbidity, mortality and cost of drug-induced illness abound in the medical literature (15,16) and the available evidence suggest that ADR represent an important health hazard (6).

The epidemiological methods employed by the Boston Collaborative Drug Surveillance Program (BCDSP) have been briefly described above (6). The data for the example to be used here were derived from 9 hospitals in the United States, Canada, Israel and New Zealand. In one of such study the CNS toxicity of diazepam, chlordiazepoxide and phenobarbital were assessed. Smoking histories and histories of ingestion of alcohol, coffee, and tea were obtained from 2322 patients who received diazepam, chlordiazepoxide or phenobarbital for anxiety. If a patient received more than 1 of the 3 drugs, only the one which he/she was first exposed was considered. In this group of patients, severe central-nervous-system depression was the most common adverse effect observed. The indicator of CNS depression accepted for analysis was clinically significant drowsiness attributed to 1 of the 3 drugs (17).

Drowsiness was more common with increasing doses of both diazepam and chlordiazepoxide. For example, the percentage of patients with drowsiness attributed to diazepam when it was used in less than 10mg was 4.1%. The percentage increased to 8.6% when diazepam doses were 10-19mg and to 11.2% when diazepam dose was higher than 20mg.

A relationship could also be found when recipients of the two drugs were further divided into non-smokers, light smokers and heavy smokers. For both diazepam and chlordiazepoxide, drug-attributed drowsiness became less common as the exposure to cigarettes increased, suggesting that one or more of the constituents of cigarette smoking may stimulate more rapid metabolism of the benzodiazepines (17).

Another example comes from our own work at the University of Chile on adverse reactions to furosemide during hospitalization. The frequency of AR was significantly related to both the daily dose of furosemide and to the total dose (18). In 553 patients receiving furosemide for different indications, the frequency of adverse reactions was significantly ($p < 0.001$) related to daily furosemide dose: ADR were present in 31.5% of patients receiving less than or equal to 40mg of furosemide . The percentage of patients with ADR increased to 37.9% if furosemide dose was 41-80mg and to 54.5% if the dose was greater that 80mg of furosemide. The frequency of adverse reactions was also significantly ($p < 0.001$) related to the total dose of furosemide.

In addition, in the same paper discussed above in which Greenblatt et al (8) showed that the efficacy of flurazepam therapy was dose-related, they also showed that the frequency of adverse reactions to flurazepam increased significantly with dose and age. Adverse reactions to flurazepam, predominantly unwanted residual drowsiness, increased with average daily doses, ranging from 1.3% among those receiving less than 15mg/day to 12.3% at doses of 30mg/day or more ($p < 0.001$).

Overdose. Psychotropic drugs are often used for self-poisoning. Therefore, drug overdose is another measure of drug morbidity and of the risks associated with drug use.

Benzodiazepines are the drugs most frequently used for overdose purposes (19). Clinical features of benzodiazepine overdose are usually mild and only supportive therapy is necessary. In a prospective epidemiological study in which nurse research assistants collected data during a 6 month period on all patients who came to 21 Toronto Hospitals with drug overdose, 1201 (34%) had ingested benzodiazepines (20). Data collected included demographic and clinical characteristics of patients, drug(s) used, quantity (dose) ingested and 'treatment' of the overdose. In this study patients who overdosed on benzodiazepines were admitted to hospital less frequently and had less disturbances of consciousness than those who used other drugs, thus supporting the view that benzodiazepines are safe drugs with respect to overdose.

Although most patients were alert at arrival to hospital, a relationship between amount of diazepam ingested and state of

consciousness on arrival was clearly observed. The higher the dose of diazepam ingested, the higher the likelihood that a patient would arrive drowsy or unconscious.

Direct Toxicity (Organ damage). Some of the best epidemiological examples of the effect of dose on drug toxicity are in the field of direct toxicity to organs by drugs of abuse, including alcohol abuse and cigarette smoking. COHORT and CASE-CONTROL studies are available. Both positive and negative associations of disease outcome, depending on the drug dose, have been reported.

The association between alcoholism and liver cirrhosis is no longer a matter of controversy. There is no doubt that alcohol consumption, assessed either by the annual per capita consumption (a very crude parameter) (21,22) or by more controlled methods (such as total life-time alcohol consumption)(23) is associated with cirrhosis mortality. Dose-response relationships are clearly observed whether dose is measured by total amount of ethanol per kg of body weight or by duration of alcohol intake, an expression of cumulative ethanol dose.

In a classic study by Lelbach, the histologic results of two groups of 108 cases, each matched for age, duration of drinking and body weight and different only on their average daily alcohol intake were compared. Group 1 had an average daily intake of 126g for ethanol and group 2 of 222g. The number of cases with potentially precirrhotic lesions was double (33%) in Group 2 compared to Group 1 (14%). Whereas no case of cirrhosis could be found in Group 1, cirrhosis morbidity was 14% in Group 2 (24).

Another way of measuring the dose of alcohol is by using the lifetime exposure to alcohol. Again, a clear dose-response relationship between mean duration of alcohol abuse and patients developing liver cirrhosis is evident. Three hundred and thirty four alcoholics classified according to duration of alcohol consumption: (a) 1-5 years; (b) 6-10 years; (c) 11-15 years; and (d) more than 15 years. Arranging the cases in this manner made it quite clear that the relative frequency of cirrhosis in the sample did rise almost linearly with increasing duration of excessive alcohol use (25).

On the other hand, alcohol use in small amounts has been associated with reduced mortality from coronary heart disease. The relationship between alcohol consumption and mortality was examined in a COHORT STUDY of 1910 men aged 38-55 years enrolled in the Albany Study, a prospective investigation of factors related to cardiovascular disease (26). Coronary heart disease was not associated with drinking at the 18-year follow-up either in univariate or multivariate analysis but was negatively associated with drinking the 28-year follow-up. Men drinking less than 30 oz per month consistently had the lowest death rates for coronary heart disease both among smokers and non-smokers although cigarette smokers had twice the mortality rate of non-smokers (26).

We will give one example of dose response relationship and direct toxicity assessed by CASE-CONTROL STUDIES. A positive correlation has been found between myocardial infarction in women and cigarette smoking, (dose expressed as cigarettes per day), with risk estimates elevated 10-fold for heavy smokers (>25 cigaretts per day) (27). The relative risk for myocardial infarction was 1 for a never smoker and 0.89 for an ex-smoker and increased to 3.47 for women smoking 1-14 cigarettes per day, to 8.93 in those smoking 15-24 cigarettes per day and to 12.42 in those women smoking more than 25 cigarettes per day ($p < 0.01$). The increased risks were similar in younger (<45 yrs) and older subjects and were not affected by other distorting factors.

Behavioural Toxicity. Among the social and public health risks associated with drug use is a failure to detect normal environmental cues that regulate a person's behaviour. There is an extensive literature dealing with drug effects on several human behaviours, including psychomotor performance and different cognitive functions, which can now be precisely measured.

Most studies of behavioural toxicity, however, are performed in the laboratory but a few human behaviours affected by drugs have been measured in large populations. For example, in laboratory experiments different doses of several drugs have been shown to impair psychomotor skills related to driving. A strong, positive association between increasing blood alcohol

concentrations and the risk of crash involvement has been documented by researchers by many decades (28).

However, the relationship between amount of ingested alcohol and severity of injury to driver has been more difficult to document, mainly because the independent measure of alcohol intoxication (blood alcohol levels) (BAC) in large populations was difficult to perform. The introduction of objective measures either by breath or blood tests is now routine in many countries and therefore, epidemiological data on alcohol dose (measured as BAC) and impaired psychomotor performance (measured as the severity of injuries in car accidents) is available.

In a study of data on all drivers involved in traffic crashes in North Carolina between 1979 to 1983, the drinking driver was more likely to suffer serious injury or death compared to the non-drinking driver. Of the 1,136,500 crash involved drivers meeting the study criteria, 21,020 had measured BAC. Treating BAC as a continuous variable, models of serious and fatal injury rates were fit to the data. Good fits to the data were obtained as an exponential function of the square of BAC, both for seriously injured drivers and impaired drivers. In both cases, injury rates increased very slowly for lower values of BAC and more rapidly for higher values (29).

Another example shows the relationship of alcohol consumption and aggression. BAC were obtained in 362 of 470 victims of assault attending an emergency room. Severity of injury was categorized in 5 categories of increasing severity. Category I being heamatoma and Category V multiple fractures. When recent consumption of alcohol was taken into account, patients consuming higher doses of ethanol tended to have more severe (category IV and V) injuries than those drinking less alcohol or abstinent (30).

META-ANALYSES

In recent years a new type of research, termed meta-analysis, has attempted to analyze and combine the results of previous reports, particularly randomized clinical trials. Meta-analysis forces systematic thought about methods, outcomes, categorizations, populations and interventions. In addition, the combination of data from several studies increases generalizability and statistical power. Furthermore, it

improves the estimates of effect size (31,32). However, this methodology is still controversial because of the many biases including validity of pooling data, non-random selection of studies and multiple tests of the same data (31,32). Many think that sophisticated statistics will not improve poor data but provide an unwarranted sense of scientific validity (31). However, since this process is increasingly used, it justifies comment and attempts should be made to recognize its limitations and identify clinical applications.

CONCLUSION

The dose-response relationship has been examined in the context of epidemiological studies.

Dose-related effects can be detected by epidemiological methods both when assessing the efficacy of drugs and also when evaluating drug toxicity. Epidemiological methods such as cohort and case-control studies are much better developed to evaluate toxicity while assessment of drug efficacy using such methodologies is still incipient.

Clear examples of a dose-response relationship evaluated by epidemiological methods can be found in different areas of drug toxicity assessment, including adverse drug reactions, overdoses, direct toxicity to organs and behavioural toxicity.

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Discussion - An epidemiological approach to dose-response relationships

L. Lemberger

Have epidemiological studies aimed at discovering potential new indications for a drug ever been undertaken?

U. Busto

Probably yes, but not necessarily addressing the dose-response relationship.

L. Lasagna

I wonder if the neglect of efficacy measurements by epidemiologists is not more a matter of tradition and bias, than of lack of definitions. For example, why can't one use the same definitions that one uses in controlled clinical trials in trying to quantify benefit in epidemiological data? I don't quite see why one needs a new set of definitions.

U. Busto

I agree with you. However, epidemiological studies traditionally concentrate on the diseases. I am not sure that we look as carefully at benefit as we do at risk.

R.J. Temple

I think the trouble with looking at effectiveness, and particularly at dose-effect relationships in epidemiological studies is that there are a lot of confounding factors. There is probably more diligent treatment in people who are sicker, and one would guess, for example, that people on higher doses of anti-hypertensives probably were less well controlled than people who were on lower doses. So the task is quite difficult, but the approach ought to work just fine if one were looking at something completely unexpected and unrelated to the purpose of using the drug in first place.

A. Reinberg

Can one envision using special tools that could provide information about confounding factors? The quality of data in a

clinical trial can easily be assured, but this is not always the case in epidemiological studies.

U. Busto

This is one of the limitations of epidemiological studies. There are many variables to be considered. I agree with you that in many cases clinical trials have much better controls than epidemiological studies, because you follow the two groups very closely. Clinical trials are experimental and epidemiological studies are mainly observational. The quality of the data is not the same. But, the fact that you can detect dose-response relationships using epidemiological methods is the objective of our discussion, and I illustrated the possibilities of the epidemiological approach for detecting dose-response effects.