Dose-response relationships in clinical pharmacology.
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DOSE-RESPONSE RELATIONSHIPS IN DRUG DEPENDENCE IN HUMANS

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I. INTRODUCTION

The addictive potential of a drug depends on several factors (e.g., intrinsic pharmacological activity of drug, dose, pharmacokinetic properties, etc.). Dose is a major determinant of substance abuse. However, studies specifically assessing the relationships between the dose of a drug and the risk for abuse potential and/or the development of dependence are rare. There are several phenomena associated with drug abuse and dependence in which the dose of the drug must be considered. In this paper we will focus on the following: a) definitions of the relevant concepts; b) factors determining the development of drug abuse and dependence; c) the effects of dose on abuse potential of a drug; d) the effects of dose on dependence liability (i.e., withdrawal reaction) of a drug; and e) the importance of dose in the treatment of the manifestations of substance abuse (e.g., treatment of the withdrawal syndrome and the use of drugs to reduce substance abuse).

Definitions

Throughout this paper we will use the following definitions which are based on standard substance abuse terminology (1):

Drug abuse is the use of any substance--other than alcohol--that has no recognized medical use, or the inappropiate use (in terms of indication or dose) of a medicinal substance in a manner detrimental to the individual or society but not meeting the criteria for drug dependence. While many drugs may be abused, the term is conventionally applied to psychoactive drugs.

Drug dependence may develop as a result of chronic drug abuse and it is divided into psychological and physical dependence.

Psychological dependence is the emotional state of craving a drug either for its positive effect or to avoid negative effects associated with its absence.

Physical dependence is a physiological state of adaptation to a drug, usually characterized by the development of tolerance to drug effects and the emergence of a characteristic set of withdrawal symptoms (often called the "abstinence syndrome") during abstinence.

Addiction is the compulsive use of a substance, resulting in physical, psychological, or social harm to the user and continued use despite that harm.

Tolerance is physiological adaptation to the effect of drugs, so that effects diminish with constant dosages or increasing doses are needed to accomplish the same desired effect. It is commonly observed with narcotics, alcohol, barbiturates and benzodiazepines. **Tolerance** is usually divided into central (due to CNS adaptation) and metabolic (due to increased drug metabolism).

Cross-tolerance is the acquisition of tolerance to other drugs after the abuse of a substance (e.g. alcohol and CNS depressants).

Abuse potential refers to those properties of a drug that are critical to the maintenance of compulsive, drug-seeking behaviour.

Dependence liability refers only to the ability of the drug to produce a withdrawal syndrome upon cessation of chronic drug administration.

II. FACTORS INFLUENCING THE ADDICTIVE POTENTIAL OF DRUGS

2.1 Biological Factors

Humans differ markedly in their potential to become dependent on drugs (2). There is evidence for genetic predisposition to alcohol consumption in rats and mice (3), as

well as humans (4, 5). Age and sex have also been associated with differences in drug ingestion (6).

2.2 Environmental Factors

Environmental conditions such as stress and nutrition are important determinants of drug-taking behaviour (7). Food-deprived rats, for example, increase their ethanol consumption (8). There is limited experimental data to support the assumption that stressful environments enhance drug-taking behaviour (7). However, cultural factors may play a major role in drug abuse. For example, the abuse of some substances is more prevalent in some cultures than in others (e.g. alcohol).

2.3 Pharmacological Action

The intrinsic pharmacological action(s) of a drug is the major determinant of whether a substance will be persistently taken (7, 2). Evidence includes correspondence within and among drug classes with respect to receptor affinity, intensity of self-administration by animals, extent of substitution in physically dependent animals, generalized preference testing and appearance of withdrawal. In this respect, there is a good relationship between the drugs that animals self-administer and those abused by humans (7).

2.4 Drug Dose

Drug dose (concentration) is important for the acquisition and maintenance of drug-taking behaviour. For example, the number of intravenous injections of pentobarbital taken in each experimental session increased as the injection dose decreased, presumably to maintain the same reinforcing effect (9). This inverse relationship between the number of intravenous injections and doses has also been shown for other drugs (10). Animals increase the dose of drugs for which tolerance develops quickly, such as morphine; whereas with cocaine, doses tend not to escalate (2).

2.5 Market Availability

It includes extent of use (market penetration) and duration of use. Provided that drugs have the intrinsic pharmacological

activity that determines abuse, their availability plays a major role in influencing the extent of abuse (11).

2.6 Patterns of Drug Abuse

Another patient factor which may play a role in determining persistent drug self-administration is pattern of use (i.e. intermittent vs. regular), prior use of the same and/or similar drugs, and other drug experiences (12).

2.7 Pharmacokinetic Factors

The pharmacokinetic properties that presumably contribute to persistent self-administration and abuse of drugs can be grouped into those that relate to acute "reinforcing" effects of a drug and those important to the development of physical dependence and the occurrence of withdrawal upon cessation of drug use (13).

To induce physical dependence, a drug must be present in high enough concentrations and remain (or be renewed) in the body long enough to permit adaptation to develop. Therefore, the kinetic determinants of drug concentration (i.e. dose, bioavailability, dosing interval, half-life and free drug clearance) are important.

A withdrawal syndrome will be observed in patients exposed to the drugs long enough to permit physical dependence to develop and in those patients using drugs associated with the development of tolerance. The rate of appearance and severity of the withdrawal syndrome will depend upon the degree of physical dependence and the apparent rate of drug removal from its site of action. Consequently, a withdrawal reaction will be more likely to manifest in patients taking drugs which are rapidly eliminated, preventing the body from responding with adaptive biochemical processes which may reverse the physical dependence state.

Drug self-administration is enhanced by rapid delivery of the drug to the CNS, whether by rapid absorption from the stomach or mucous membranes, by intravenous injection, or by virtue of high lipid solubility or very small molecular size (e.g., cocaine and heroin).

Ethanol--with rapid absorption, rapid entry into the brain, a relatively wide margin of safety, pleasant pharmacological

actions, a multiplicity of CNS effects and high clearance--meets virtually all pharmacokinetic and pharmacological criteria for a drug of high abuse potential.

III. DOSE AND ABUSE POTENTIAL IN HUMANS

Abuse liability refers to those properties of a drug that are critical to the maintenance of compulsive, drug seeking behaviour. Abuse potential is evaluated in humans using two main paradigms: a) indirectly by assessing the subjective effects of a drug after its administration; and b) directly by assessing the reinforcing effects of drugs by comparing preference among the presumed drugs of abuse and a placebo. Both paradigms have been used to assess dose response relationships in substances of abuse, as described below.

3.1 Quantification of Subjective Effects

Although the issue is controversial, subjective effects are usually considered critical indices for predicting abuse potential. The basic technique for the objective measurement of subjective effects is the single-dose drug administration procedure, which involves subjects who have previously used and abused psychoactive substances (14). The procedure yields reliable data because drug abusers are able to discriminate between psychoactive substances and placebo, thereby providing stable control data. Single doses of drugs are given at sufficient time intervals to eliminate residual drug effects using a double-blind procedure, and a variety of signs and symptoms are assessed. Typically, two or more doses of the test compound are compared with placebo and an appropriate positive control (such as pentobarbital in the study of sedatives) in a cross-over design with approximately 10 subjects. Data are expressed as changes from the pre-drug (baseline) and observations are averaged across subjects. Depending on the temporal pattern, drug effects may be expressed as either peak effect or as the area under time-action curve. Among several subjective measurements, the crucial item is the 5-point "liking" scale which measures euphoria (14).

A variety of drugs have been assessed with this methodology. Drugs known to produce widespread compulsive use, such as morphine, d-amphetamine, and pentobarbital produce dose-

related increases in "liking" scores, whereas other substances not known to be abused (e.g. chlorpromazine, zomepirac or placebo) do not significantly increase "liking" scores. One of the limitations of these studies is that since usually several doses of the drugs are not tested, the dose-response curve is not fully assessed. In addition, it has been argued (15) that since these studies do not directly measure self-administration of the substance of abuse their validity is limited. Recently, however, it has become a standard procedure to incorporate measures of subjective effects as well as direct measures of self-administration in studies assessing abuse potential (15).

3.2 Reinforcing Effects

Dose-response relationships with respect to abuse potential have also been explored in the drug preference paradigm. In such a paradigm subjects with a documented history of drug abuse are hospitalized in a residential ward unit and a placebo, a positive control drug and the test substance are available for oral ingestion. The effects and the maintenance of self-administration of the various drugs are assessed (16, 17). As an illustration we will summarize studies evaluating the reinforcing effects of barbiturates and benzodiazepines. Fourteen placebo-controlled, double-blind experiments in subjects with histories of drug abuse have demonstrated that benzodiazepines produce dose-related reinforcing (i.e. maintain self-administration) and/or subjective effects indicating some potential for abuse (16). These results have been obtained with several benzodiazepines (diazepam, triazolam, oxazepam, prazepam, halazepam, lorazepam and chlordiazepoxide), which have different pharmacokinetic profiles (rapid versus slow onset of effects, fast versus slow elimination), and clinical applications (anxiolytic versus hypnotic).

However, in studies of a similar design, healthy volunteers failed to maintain self-administration of low doses of benzodiazepines (e.g., diazepam 10 mg) (18), suggesting that only the high doses are reinforcing.

Eight studies comparing the reinforcing/subjective effects of a benzodiazepine (diazepam, chlordiazepoxide or triazolam) with those of pentobarbital showed that the barbiturate had

greater liability for abuse. These results are consistent with animal self-administration data.

There may be meaningful differences in the reinforcing/subjective effects of various benzodiazepines. Specifically, lorazepam appears to be similar to diazepam, whereas oxazepam, halazepam and chlordiazepoxide may have less liability for abuse than diazepam (16). When diazepam and oxazepam were compared, diazepam (10 to 160 mg) produced greater liking and euphoria than oxazepam (30 to 480 mg) and was judged to be of greater monetary street value. Diazepam's rapid onset of effect was repeatedly cited as being a desirable feature. In addition, behavioural choice tests showed that diazepam was a more efficacious reinforcer than oxazepam. Similar differences have also been observed with barbiturates such as pentobarbital and secobarbital (16).

Epidemiological studies, controlling for extent of drug use, have also confirmed that diazepam has a greater abuse potential than oxazepam, approximately in the order of 2:1 (12, 19).

IV. DOSE AND PHYSICAL DEPENDENCE IN HUMANS

The severity of the abstinence syndrome will generally vary with the dose of the drug of abuse. The more severe symptoms will occur in subjects who have been abusing large doses for a prolonged time. Systematic studies relating various doses of a drug and the severity of the withdrawal syndrome are unavailable. However, we can still assess the effect of dose by observing the manifestations of the withdrawal syndromes occurring in subjects who have been studied separately after they have taken high or low (therapeutic) doses of benzodiazepines. We will focus on these drugs because they are commonly used/abused and because we have been particularly interested in the study of their clinical effects.

4.1 Benzodiazepine Physical Dependence Following High Dose Use

In the classic study (20) 11 psychotic patients were abruptly switched to placebo after receiving high daily doses of chlordiazepoxide (300 to 600 mg/day, 8 to 20 times the usual therapeutic dose) for 2 to 6 months. Withdrawal signs, (e.g., depression, aggravation of psychosis, agitation, insomnia, loss

of appetite and nausea) appeared within 2 and 8 days in 10 of the 11 patients. Two patients had grand mal seizures on days 7 and 8.

These findings have been confirmed and extended to other benzodiazepines (21, 22). For example, 10 patients who had used high doses of diazepam for 3 to 14 years (23) developed withdrawal syndromes, lasting up to 6 weeks, on termination of drug dosing. Although there were no convulsions, alcohol- or barbiturate-like delirium occurred in 4 subjects during the first 10 days of withdrawal. Minor symptoms included anxiety, insomnia, agitation, anorexia, tremor, muscle twitching and perceptual changes such as paresthesias and hypersensitivity to light and noise.

4.2 Benzodiazepine Physical Dependence Following Therapeutic Doses

Benzodiazepines can also produce physical dependence after prolonged treatment at therapeutic doses (24). The profile, intensity and time course of signs and symptoms occurring after discontinuation of drug suggest that they are not a simple re-emergence of pre-existing anxiety or insomnia. Although the most severe withdrawal signs (seizures and delirium) are generally absent in therapeutic dose dependence, anxiety, insomnia, irritability, tremor, muscle twitching, headache, gastrointestinal disturbance, depersonalization and the above-mentioned perceptual changes remain.

In an effort to determine the existence of a withdrawal reaction after prolonged use of therapeutic doses of benzodiazepines we conducted a double-blind, placebo controlled study in forty patients who were long-term therapeutic users of benzodiazepines (24). Subjects were randomly assigned to receive placebo or diazepam in a dose approximately equivalent to their usual dose of benzodiazepines. The dose of diazepam (or placebo) was then tapered off during an eight-week withdrawal period. All subjects received the same behavioural treatment with a goal of abstinence, emphasizing the development of strategies for coping with abstinence.

The subjects who received placebo had more symptoms, rated their symptoms as more severe and dropped out from the experimental condition at a higher rate than those receiving a tapering dose of diazepam. The timing and pattern of the

symptoms were consistent with a withdrawal reaction to benzodiazepines. Thus, subjects in the placebo group experienced symptoms shortly after switching to this condition, whereas those in the diazepam group had symptoms much later. Most manifestations disappeared gradually over a four-week period. No subject developed severe symptoms of withdrawal reaction (e.g. seizures). These data support the notion that dependence on low doses of benzodiazepines has a pharmacological basis, and that there is a causal relationship between discontinuation of a benzodiazepine and its self-administration in dependent persons.

V. DOSE AND THE TREATMENT OF SUBSTANCE ABUSE

5.1 Treatment of Withdrawal Syndromes

The treatment of the withdrawal syndromes associated with the discontinuation of sedative drugs such as barbiturates, benzodiazepines and ethanol has been improved by using a sound pharmacodynamic and pharmacokinetic rationale, including the application of dose-response relationships.

The procedure we have been using is termed "loading dose technique" (25). It is based on a careful titration of the dose of the drug being used. The subject is administered unit doses of the drug until a pre-determined clinical end-point is reached. This clinical end-point reflects either attenuation of the symptoms of withdrawal or signs of drug side effects. As we previously mentioned, the appearance of a withdrawal syndrome is dependent on the rate of elimination of the drug from the body; therefore the patient must receive a drug which also has a sufficiently long half-life to cover him beyond the acute phase, i.e., to provide a "pharmacokinetic umbrella". Substances which are generally effective for the management of withdrawal show cross-tolerance, are sedative-hypnotics, are anticonvulsant, and may have anxiolytic properties (25).

5.1.1 Benzodiazepine Loading Dose Technique for Treating the Alcohol Withdrawal Syndrome

Benzodiazepines are currently the drugs of choice for treating the alcohol withdrawal syndrome as they have cross-tolerance with alcohol, have superior anticonvulsant activity, do not cause enzyme induction, and are less likely to produce physical dependence, tolerance or toxicity than barbiturates

(25). Approximate equivalent doses relative to chlordiazepoxide 100 mg are diazepam 20 mg, oxazepam 120 mg and lorazepam 5 mg.

The "loading dose technique" takes particular advantage of the pharmacokinetic tapering afforded by diazepam's and N-desmethyldiazepam's long half-lives. Patients in moderate to severe withdrawal are assessed with the Clinical Institute Withdrawal Assessment-Alcohol (CIWA-A) scale, and unit doses of 20 mg of diazepam p.o. are administered hourly until the patient shows clinical improvement (decrease in CIWA-A to $\leq$ 10) or becomes mildly sedated. When a sufficiently large initial dose (at least 60 mg) has been given, additional doses are unnecessary. In a double-blind placebo-controlled study, fifty percent of patients responded to 60 mg of diazepam p.o. within 7.6 h and most of the patients improved in less than 36 h, a faster and greater average improvement than those who received placebo (26). More importantly, complications (seizures, hallucinations, arrhythmias) occurred exclusively in those treated with placebo, most likely due to delay in therapy. Diazepam blood levels peak quickly, so a large amount of the drug is available when the clinical manifestations are severe. Therefore, the benzodiazepine loading dose procedure reduces the frequency of adverse reactions and the need for further pharmacotherapy in the treatment of alcohol withdrawal.

5.1.2 Phenobarbital Loading Dose Technique for Treating Barbiturate Withdrawal

The application of similar dynamic and kinetic principles has led to the successful treatment of barbiturate- and mixed drug-abusing patients by simply giving loading doses of phenobarbital that are titrated to clinical effect and/or toxicity (27). Phenobarbital (1.7 mg/kg $\cdot$ h^{-1} by mouth) is given as unit doses of 120 mg, either until three of the following signs--nystagmus, drowsiness, ataxia, dysarthria or emotional lability--are present, or, in symptomatic patients, until the withdrawal signs and symptoms disappear. Patients are assessed carefully for evidence of intoxication and the therapeutic effect of phenobarbital before each dose is given. Some patients need hourly doses of phenobarbital for 15-20 hours but this is not a problem with hospitalization. The median phenobarbital loading dose is 1440 mg (mean $\pm$ SD, 23.4 $\pm$ 7.1 mg/kg) and the median maximum plasma concentration that is

achieved with the median phenobarbital loading dose is 35. 9 mg/l (range, 13.2-71.6 mg/l). With this regimen, no patient developed seizures or delirium and withdrawal symptoms were few and minimal. While the length of hospitalization was 11 days, medical supervision was necessary for only three days. Discharge or rehabilitation efforts are considered at 48 hours after the loading dose. In acutely ill patients, phenobarbital (0.3 mg/kg · min^{-1}) can be infused by the intravenous route to the same end-points (28).

The dose of phenobarbital that is required for treatment or to reach safe, mild intoxication is a useful diagnostic indicator of the actual extent of drug use, the severity of physical dependence on hypnosedative drugs and the likelihood of a clinically important withdrawal reaction if the patient is not treated adequately. Patients who require less than 7 mg/kg (typically 489 mg) phenobarbital to be intoxicated are, in fact, not sufficiently physically dependent on the drug to require full loading therapy or further treatment.

The loading dose technique has resulted in a marked decrease in troublesome, manipulative "drug-seeking" behaviour by patients. The systematic titration of drug dose to specific end-points over a short period of time has decreased the tendency of the clinician to respond to non-specific signs to allay the anxieties of the patient and ward staff members, as well as his or her own anxiety concerning the discomfort of drug withdrawal.

5.1.3 Treatment of Benzodiazepine Withdrawal

Similar principles have been applied to a simplified treatment of benzodiazepine withdrawal syndrome. Patients abusing benzodiazepines with short and intermediate half-lives are switched to equivalent doses of diazepam and tapered off by approximately 10% per day. This protects patients from withdrawal symptoms which occur with rapidly eliminated benzodiazepines (29).

5.2 Reduction of Substance Abuse

Recently, new pharmacological interventions have been developed to reduce substance abuse. We have been investigating the effects of serotonin uptake inhibitors in alcohol

consumption in humans (30, 31). The high doses of the four serotonin uptake inhibitors tested to date (zimelidine, citalopram, viqualine and fluoxetine) significantly decreased the total number of drinks consumed. The effect is, therefore, dose-related. Detailed descriptions of the studies are provided elsewhere (30, 31).

Conclusions:

In this paper we have reviewed the importance of the dose-response relationship with respect to the abuse liability of drugs, the development of physical dependence and the treatment of substance abuse. Relevant examples illustrated that these aspects of drug dependence are dose-related.

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Discussion - Dose-response relatıonships in drug dependence

L. Lasagna

Obviously one would like to predict the abuse potential of a new drug wıth regard to drug abusers, but the likelihood of abuse by people not inclıned to abuse drugs is also of great interest. To what extent does one get addıtional qualitative or quantitative insights into either of these kinds of predictions by combining the type of human studies that you described with behavioral pharmacological studies in animals, which are obviously quıte good ın predicting abuse liabilıty?

C.A. Naranjo

Perhaps ıt should be emphasızed why drug abusers are recruited to evaluate the abuse potentıal of new drugs. The assessment of drug abuse by either a drug-lıking or a drug-preference paradigm must take into account that these are dose-dependent phenomena. Therefore, because of the presence of tolerance to drugs and also because of ethical reasons, usually higher doses can be given to drug abusers than to healthy volunteers. With regard to animal data, particularly those obtained in self-admnistration studies, they are quite good at predicting abuse liability in man. The correlation between anımal and human data for most drugs is really very good.

L.F. Prescott

There is another factor which you did not mention, and it may be very ımportant in the context of abuse in the community. I am thinking here of the cultural, social and group activitıes which tend to draw people ınto drug usage.

L. Lemberger

Could you comment on the problems posed by differences in response to drugs by drug abusers?

C.A. Naranjo

There is data, some anecdotal and other coming from well designed studies, showing that many CNS drugs exhibit cross tolerance wıth ethanol and, of course, the response to them will be

diminished in an alcoholic. On the other hand, some drugs of abuse act as enzyme inducers and a reduced response to drugs that may have enhanced metabolism can be envisaged in subjects abusing them.

M. Orme

Analog rating scales have been used in the quantification of subjective effects. In the case of pain analog scales used in arthritic diseases, it has been shown that if one marks out the middle, people tend to group their results very close to this mark. Does the same happen in studies about "liking"?

C.A. Naranjo

No. Our data tend to show a distribution around the middle point. For example in our studies with serotonin uptake inhibitors we have even been able to detect changes in the "liking" of substances of abuse. Furthermore, the "liking" scales are remarkably useful to discriminate between different doses of a drug.