

Dependence, Tolerance, and Addiction to Benzodiazepines: Clinical and Pharmacokinetic Considerations*

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I. INTRODUCTION

Benzodiazepine derivatives are among the most widely used pharmacologic agents in the Western world. Some 10 to 20% of ambulatory adults in the United States and other Western nations ingest benzodiazepine derivatives on a regular basis due to anxiety, tension, or insomnia [1, 2]. Given the widespread extent of benzodiazepine use for therapeutic purposes, the issue of benzodiazepine misuse is of considerable medical and social importance. Unfortunately, achievement of a rational clinical perspective of this problem has been made nearly impossible by a barrage of irresponsible and sensationalistic journalism by popular newspapers, periodicals, and television. This review considers clinical and pharmacokinetic evidence relating to tolerance, habituation, and addiction to benzodiazepine derivatives. Emphasis is placed upon the clinical implications of research findings.

II. SORTING OUT TERMINOLOGY

The terms tolerance, addiction, habituation, and dependence are subject to much misunderstanding. Furthermore, they carry unfortunate connotations that associate them with "hard-core" drug addiction. Reasonably precise definitions for these terms must be developed prior to discussion of any specific clinical problem [3-5]. Our definitions are only operational, developed to facilitate and clarify understanding of the problems discussed within this particular article.

Addiction is used synonymously with physiologic dependence, and denotes a syndrome of physiologic drug dependence. Addiction generally follows prolonged drug exposure, although the length of time necessary to develop addiction varies greatly among classes of drugs. True addiction is not present unless drug discontinuation is

followed by an objective withdrawal syndrome, characterized by objective physiologic changes. Habituation, or psychological dependence, may coexist with true addiction, but this is not necessarily the case. The habituated individual craves or desires drug exposure, and experiences unpleasant subjective sensations when deprived of the drug. However, objective withdrawal syndromes do not occur unless habituation coexists with addiction. Again, habituation is generally associated with long-term drug exposure. Tolerance is of two major types, either or both of which may coexist with habituation or addiction. Receptor-site tolerance really means adaptation, and refers to the effect that duration of exposure of the central nervous system (CNS) receptor site to any given drug concentration may have upon the clinical and physiologic manifestations of the drug-receptor interaction. That is, a given CNS receptor-site drug concentration may have a different effect depending on how long and in what concentration the receptor has been exposed to the drug. This type of tolerance usually tends to reduce clinical drug effects as the duration of drug exposure proceeds. A common example involves the acute intoxicant effects of ethyl alcohol. The alcohol concentration in the blood (and presumably also at the receptor site in the brain) following acute ingestion of ethanol may be higher during recovery from acute intoxication than earlier when subjective manifestations of intoxication are maximal. Pharmacokinetic or metabolic tolerance, on the other hand, denotes the effect of prolonged drug exposure upon its own pharmacokinetic properties. The term usually describes the phenomenon of increased drug clearance associated with repeated ingestion, as in the case of prolonged barbiturate exposure. The clinical consequence of this is that steady-state blood concentrations of a drug administered on a chronic basis will progressively fall despite continued administration of the same dose.

The following sections review the relation of these definitions to published clinical studies on benzodiazepine derivatives.

III. ADDICTION

Reliable reports of true addiction to benzodiazepine derivatives do exist. The first such report was published by Hollister and associates [6] in 1961. They administered chlordiazepoxide, 100 to 600 mg daily, to 36 hospitalized psychiatric patients for periods of 1 to 7 months. Eleven patients were abruptly changed to placebo on a single-blind basis. Ten of the 11 developed objective or subjective signs of withdrawal,

including depression in six, worsening of psychosis in five, insomnia and agitation in five, decreased appetite in four, seizures in three, and twitching in one. Most symptoms appeared 4 to 8 days after drug discontinuation, and had largely subsided by the tenth day. Between 1963 and 1972, an additional nine case reports were published [7-15] (Table 1). Several further reports have appeared since this time [16-22], including descriptions of apparent withdrawal syndromes in neonates following maternal exposure to benzodiazepines [23, 24]. The characteristics of subsequent reports generally are similar to the description by Hollister and associates [6]. The majority of patients had been ingesting very large doses of the drugs for extended periods of time. Signs and symptoms of withdrawal resembled those associated with discontinuation of any sedative-hypnotic agent to which addiction has developed, and ranged from agitation, tachycardia, and diaphoresis to more serious consequences such as hallucinations, psychosis, and seizures. With the exception of oxazepam, benzodiazepine derivatives clinically available in the United States through 1976 are characterized by a long duration of action and/or the presence of pharmacologically-active metabolites [25, 26]. This probably explains why symptoms of withdrawal generally do not appear until several days after drug discontinuation.

Although these case reports constitute valid observations, they provide little or no perspective on the incidence or extent of benzodiazepine addiction. Unfortunately, case reports such as these often are taken out of context and portrayed as everyday occurrences by the popular media. Considering the extent of use of diazepam and other benzodiazepines, true addiction is probably exceedingly unusual, and when it occurs is probably confined to those individuals with "addiction-prone" personalities who ingest very large doses [27]. There are few systematic studies of problems associated with benzodiazepine withdrawal following ingestion of therapeutic doses. Covi and associates [28, 29] investigated the effect of abrupt discontinuation of chlordiazepoxide (45 mg/day) after long-term treatment. Their findings suggested that a mild abstinence syndrome, consisting mainly of subjective feelings of anxiety and tension as well as minor symptoms (such as trembling, poor appetite, and faintness or dizziness) may be a consequence of chlordiazepoxide withdrawal in some individuals who had taken the drug continuously for 20 weeks. It should be emphasized that such manifestations can be very difficult to distinguish from recrudescence of the original anxiety-related symptoms for which the drug was initially prescribed.

On the basis of currently available evidence, it seems that widespread concern about benzodiazepine addiction is based largely upon irresponsible journalism rather than sound scientific evidence [27, 30].

IV. HABITUATION

There is little reliable data on the nature and extent of habituation or psychological dependence associated with benzodiazepine treatment. Many individuals ingest these drugs over long periods of time, but this certainly does not imply true habituation nor that their use of these derivatives is inappropriate, excessive, or dangerous. In the vast majority of cases it is likely that long-term benzodiazepine use reflects the continued presence of symptomatic anxiety or insomnia, which would recur and lead to considerable emotional discomfort were the drugs discontinued. Winstead and associates [31] studied the "habituating" potential of diazepam in a series of hospitalized psychiatric patients who were allowed "free access" to diazepam. Patients could receive diazepam on request in doses of up to 10 mg every 4 hr. The availability of diazepam did not lead to excessive drug-seeking behavior nor was there evidence of development of dependence. The 83 patients studied over a 6-month period requested diazepam on the average of once every 3 days, and 27% of patients never requested the drug. Hubbard and Kripke [32] studied the extent of flurazepam use among discharged psychiatric patients. Outpatient flurazepam use was no more common among those who had received the drug while hospitalized than in those who did not, suggesting that in-hospital flurazepam prescribing did not lead to dependence.

Data on benzodiazepine habituation by drug abusers is largely anecdotal. We are commonly told that diazepam is a "street drug" and that it ranks high among drugs of abuse [22, 33, 34]. However, reliable documentation of this is lacking. Estimates of the incidence of benzodiazepine abuse must always be considered in the context of its extensive use for therapeutic purposes and the easy availability of the compound.

It may be very difficult to distinguish psychological dependence from true physiologic addiction. Adam and associates [35] studied the effect of nightly ingestion of nitrazepam (5 mg) for 10 weeks upon sleep patterns and subjective responses of 10 volunteers aged 41 to 62 years. The mean total sleep duration during the nitrazepam treatment period increased significantly over the pretreatment control period. However, after nitrazepam withdrawal the average total sleep duration was less than that during the prenitrazepam baseline condition. The findings suggest that withdrawal of nitrazepam following prolonged use leads to impairment of total sleep duration. However, the subjective nature of the withdrawal experience was not discussed. The findings do not establish whether prolonged nitrazepam use leads to physiologic dependence (addiction), psychological dependence (habituation), or both. It is evident that considerable uncertainty exists in this area.

TABLE 1
Case Reports of Addiction to Benzodiazepines

Refs.	Patient characteristics (age, sex)	Drug	Dose (mg/day)	Duration	Result
7	52, female	Diazepam	40-60	3 months	Acute delirium tremens-like syndrome upon discontinuation of drug
8	39, female; history of barbiturate and alcohol abuse	Diazepam	Maximum of 500	Weeks	Diazepam withdrawal syndrome suppressed by ethanol
9	51, male	Nitrazepam	20 mg nightly	Years	Acute delirium tremens-like syndrome upon discontinuation of drug
10	23, female	Diazepam	60	1 year	Tremulous, diaphoretic, and agitated upon discontinuation of drug
11	44, female	Chlordiazepoxide	160	Dosage increased over 2 months	Withdrawal syndrome prevented by trifluoperazine

12	29, male	Oxazepam	90	18 months	Severe agitation and depression upon discontinuation of drug
13	20, male, with dystonia musculorum deformans	Diazepam	40-60	11 days	Severe withdrawal syndrome and death 3 days after drug discontinuation
14	29, female	Oxazepam	400-600	6 weeks	Acute toxic delirium 5 days after discontinuation of drug
15	37, female	Chlordiazepoxide	50-140	Years	Abdominal pains, diaphoresis, hallucinations upon discontinuation; symptoms suppressed by reinstating drug

We recommend that physicians discuss these issues with all patients who are initiating benzodiazepine therapy. They are best told that treatment is likely to cause some symptomatic relief of their emotional disturbances, and that discontinuation of treatment may be followed by reappearance of symptoms. It is our practice to reassure patients that true addiction is unlikely, and that the hazards of benzodiazepines as depicted by the popular media are greatly exaggerated.

V. RECEPTOR-SITE TOLERANCE

Although habituation and addiction to benzodiazepines appears to be very uncommon, some degree of receptor-site tolerance or adaptation probably occurs in every individual exposed to the drug. Considerable circumstantial and clinical evidence supports this impression. We have observed that subjective perceptions of feeling "spaced out" or reduction in the speed and clarity of thought processes following single 25-mg oral doses of chloridazepoxide depend more upon the rate at which blood levels are achieved following the dose than upon the blood level measured at the time that the subjective effect is assessed [36]. MacLeod and associates [37] have found that the extent of psychomotor impairment attributable to a single oral dose of diazepam is far greater on the "upswing" of the curve than on the "downswing" of the curve, even though plasma levels at the time of testing may be similar. These findings support the clinical importance of drug absorption rate or the rate of change of drug levels as important determinants of subjective and objective clinical effects. Similar findings are reported by Bliding [38] in a comparison of diazepam and oxazepam.

Clinical observations on the time course of subjective sedative effects following single and multiple doses of benzodiazepines further support the concept of adaptation. Individuals initiating diazepam therapy often feel subjective drowsiness during the first day or two of treatment. If the same dose is continued, the sensation of drowsiness may abate [39] even though there is extensive drug accumulation [39-42]. Blood concentrations of diazepam and desmethyl-diazepam at the time that drowsiness has essentially disappeared may greatly exceed those measured during the early part of therapy when drowsiness was symptomatically evident. The findings are similar with single- and multiple-dose flurazepam therapy. After a single oral dose of flurazepam, little or no unchanged flurazepam is measured in the bloodstream. However, there is a gradual increase in levels of desalkylflurazepam, a pharmacologically active metabolite,

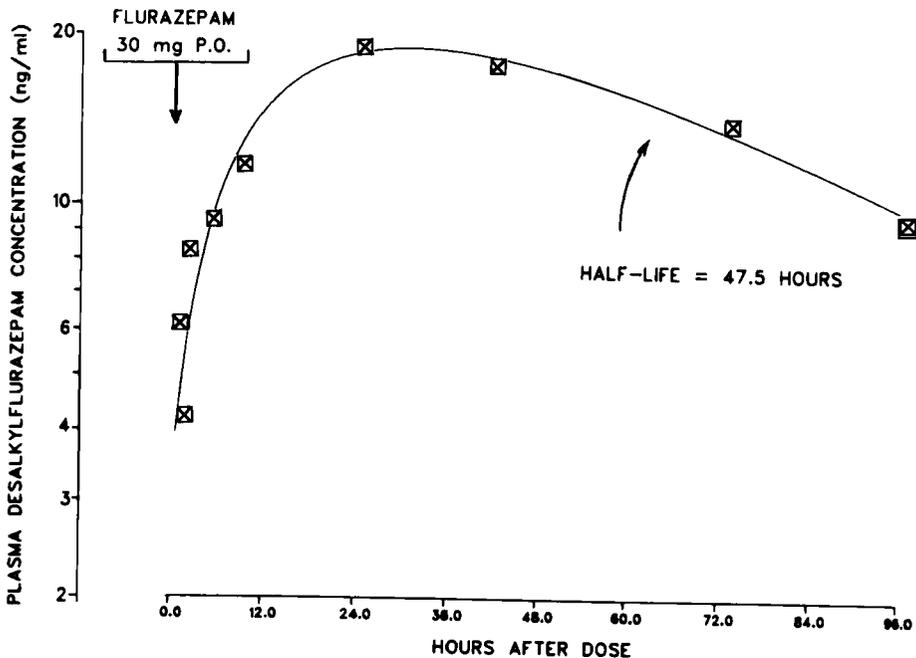


FIG. 1. A healthy male volunteer ingested 30 mg of flurazepam hydrochloride (Dalmane), following which multiple venous blood samples were drawn over the next 4 days. Plasma samples were analyzed by electron-capture gas-liquid chromatography after extraction with benzene. Intact flurazepam and/or its hydroxyethyl metabolite were detected only in samples drawn during the first 2 hr, and in concentrations so low as to be barely measurable. However, relatively high concentrations of the major pharmacologically active metabolite, desalkylflurazepam, appeared in plasma. Peak levels were reached 24 hr after the flurazepam dose, and thereafter declined with an apparent half-life of 47.5 hr.

which probably accounts for its clinical effects (Fig. 1). Peak levels of desalkylflurazepam may not be reached until 24 hr after the dose, at which time patients generally perceive little or no drug effects. Repeated ingestion of flurazepam leads to continued accumulation of this metabolite [43], despite a lack of any sensation of cumulative drowsiness or sedation [44, 45]. Thus the sleep-inducing effect of

any given dose of flurazepam may be related more to the rate at which the metabolite is generated than to the absolute blood level.

Most of these observations relate to unwanted effects of benzodiazepines—drowsiness, psychomotor impairment, or excessive sedation. It appears that tolerance to the therapeutic effects of the drug develop much less readily, and that the sedative and antianxiety drug effects become dissociated with multiple-dose therapy. Thus repeated ingestion of diazepam may lead to excessive sedation early in the course of therapy. As treatment is continued at the same dose, the subjective sensation of drowsiness or oversedation abates, while the antianxiety effects remain present or even become accentuated. Unfortunately, reliable clinical documentation of the time course of these two effects is largely lacking, but the observation is well documented in animal studies [46-49].

The phenomenon of receptor-site tolerance or adaptation to benzodiazepines greatly complicates interpretation of blood levels and pharmacokinetics in relation to clinical effect. A given blood level may have one clinical effect at one time but a different effect at a later time after a period of drug exposure has elapsed. Furthermore, it is conceivable that blood concentrations and pharmacokinetic properties bear one type of relationship to nonspecific sedative effects but an entirely different relationship to clinical antianxiety effects.

VI. METABOLIC TOLERANCE

Objective pharmacokinetic and metabolic effects of long-term benzodiazepine administration are more easily studied than effects of repeated administration upon mood, effect, and psychomotor function. Animal investigations indicate that administration of large doses of benzodiazepine derivatives under certain conditions can produce enzyme induction [50]. Clinical studies, however, indicate that enzyme induction by benzodiazepines, if it occurs, is seldom of clinical significance. Several workers have found no effect of benzodiazepine derivatives upon the pharmacokinetics of phenylbutazone, antipyrine, or ethanol [50]. Vesell and associates [51] found that 7 days of prazepam administration (30 mg/day) to healthy males did not stimulate the metabolism of either prazepam itself or of antipyrine. Numerous studies indicate that benzodiazepines, unlike barbiturates, do not stimulate the metabolism of oral anticoagulants [50].

The effect of benzodiazepine treatment upon their own metabolism is controversial. Klotz and associates [52] found that the elimination

half-life of diazepam following multiple doses is prolonged in comparison with that observed following a single dose, possibly due to the inhibitory effect of the metabolite, desmethyldiazepam, upon diazepam clearance. On the other hand, the findings of Kanto et al. [53] and Sellman et al. [54] suggest that multiple-dose therapy with diazepam in humans causes induction of diazepam biotransformation. Epidemiologic studies indicate that unwanted drowsiness due to diazepam and chlordiazepoxide is more common in nonsmokers than in smokers [55], possibly because cigarette smoking stimulates the biotransformation and clearance of benzodiazepine derivatives. However, the pharmacokinetic studies of Klotz and associates [56] found no effect of smoking on diazepam clearance.

VII. COMMENT

The hazards of benzodiazepine addiction and habituation probably have been greatly exaggerated. Some individuals receiving benzodiazepines for the symptomatic treatment of anxiety or insomnia over long periods of time may experience dysphoric symptoms when the drugs are discontinued. This probably does not represent addiction or dependence, but rather reappearance of the disease for which treatment was originally initiated. Some degree of tolerance to the non-specific sedative effects of benzodiazepines probably develops in virtually all individuals who receive the drugs. This is not necessarily unfavorable, since it is not clear whether tolerance also develops to the therapeutic effects. Clinically important enzyme induction attributable to benzodiazepines appears to occur seldom, if ever. This accounts for why so few pharmacokinetic drug interactions have been reportedly associated with benzodiazepine treatment.

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REFERENCES

- [1] D. J. Greenblatt, R. I. Shader, and J. Koch-Weser, "Psychotropic Drug Use in the Boston Area: A Report from the Boston Collaborative Drug Surveillance Program," Arch. Gen. Psychiatry, 32, 518-521 (1975).
- [2] M. B. Balter, J. Levine, and D. I. Manheimer, "Cross-National Study of the Extent of Antianxiety/Sedative Drug Use," N. Engl. J. Med., 290, 769-774 (1974).
- [3] H. Isbell, "Clinical Aspects of the Various Forms of Nonmedical Use of Drugs," Anesth. Analg. (Cleveland), 50, 886-905 (1971).
- [4] H. Kalant, A. E. LeBlanc, and R. J. Gibbins, "Tolerance to, and Dependence on, Some Nonopiate Psychotropic Drugs," Pharmacol. Rev., 23, 135-191 (1971).
- [5] A. Wikler, "Dynamics of Drug Dependence: Implications of a Conditioning Theory for Research and Treatment," Arch. Gen. Psychiatry, 28, 611-616 (1973).
- [6] L. E. Hollister, F. P. Motzenbecker, and R. O. Degan, "Withdrawal Reactions from Chlordiazepoxide (Librium)," Psychopharmacologia, 2, 63-68 (1961).
- [7] H. H. Barten, "Toxic Psychosis with Transient Dismnesic Syndrome Following Withdrawal from Valium," Am. J. Psychiatry, 121, 1210-1211 (1965).
- [8] A. W. Clare, "Diazepam, Alcohol, and Barbiturate Abuse," Br. Med. J., 4, 340 (1971).
- [9] L. Darcy, "Delirium Tremens Following Withdrawal of Nitrazepam," Med. J. Aust., 2, 450 (1972).
- [10] E. B. Gordon, "Addiction to Diazepam (Valium)," Br. Med. J., 1, 112 (1967).
- [11] L. A. Guile, "Rapid Habituation to Chlordiazepoxide (Librium)," Med. J. Aust., 2, 56-57 (1963).
- [12] S. M. Hanna, "A Case of Oxazepam (Serenid D) Dependence," Br. J. Psychiatry, 120, 443-445 (1972).
- [13] R. Relkin, "Death Following Withdrawal of Diazepam," N.Y. State J. Med., 66, 1770-1772 (1966).
- [14] J. W. Selig, "A Possible Oxazepam Abstinence Syndrome," J. Am. Med. Assoc., 198, 951-952 (1966).
- [15] J. Slater, "Suspected Dependence on Chlordiazepoxide Hydrochloride (Librium)," Can. Med. Assoc. J., 95, 416 (1966).
- [16] K. Fruensgaard, "Withdrawal Psychosis: A Study of 30 Consecutive Cases," Acta Psychiatr. Scand., 53, 105-118 (1976).

- [17] D. Haskell, "Withdrawal of Diazepam," J. Am. Med. Assoc., 233, 135 (1975).
- [18] S. H. Preskorn and L. J. Denner, "Benzodiazepines and Withdrawal Psychosis," Ibid., 237, 36-38 (1977).
- [19] J. B. Floyd, Jr. and C. M. Murphy, "Hallucinations Following Withdrawal of Valium," J. Ky. Med. Assoc., 74, 549-550 (1976).
- [20] A. Rifkin, F. Quitkin, and D. F. Klein, "Withdrawal Reaction to Diazepam," J. Am. Med. Assoc., 236, 2172-2173 (1976).
- [21] P. C. Misra, "Nitrazepam (Mogadon) Dependence," Br. J. Psychiatry, 126, 81-82 (1975).
- [22] G. E. Woody, C. P. O'Brien, and R. Greenstein, "Misuse and Abuse of Diazepam: An Increasingly Common Medical Problem," Int. J. Addict., 10, 843-848 (1975).
- [23] J. L. Rementeria and K. Bhatt, "Withdrawal Symptoms in Neonates from Intrauterine Exposure to Diazepam," J. Pediatr., 90, 123-126 (1977).
- [24] P. Athinarayanan, S. H. Pierog, S. K. Nigam, and L. Glass, "Chlordiazepoxide Withdrawal in the Neonate," Am. J. Obstet. Gynecol., 124, 212-213 (1976).
- [25] D. J. Greenblatt, R. I. Shader, and J. Koch-Weser, "Pharmacokinetics in Clinical Medicine: Oxazepam Versus Other Benzodiazepines," Dis. Nerv. Syst., 36(5, Sec. 2), 6-13 (1975).
- [26] D. J. Greenblatt and R. I. Shader, "Benzodiazepines," N. Engl. J. Med., 291, 1011-1015, 1239-1243 (1974).
- [27] L. E. Hollister, "Valium: A Discussion of Current Issues," Psychosomatics, 18, 44-58 (1977).
- [28] L. Covi, L. C. Park, R. S. Lipman, E. H. Uhlenhuth, and K. Rickels, "Factors Affecting Withdrawal Response to Certain Minor Tranquilizers," in Drug Abuse: Social and Psychopharmacological Aspects (J. O. Cole and J. R. Wittenborn, eds.), Thomas, Springfield, Illinois, 1969, pp. 93-108.
- [29] L. Covi, R. S. Lipman, J. H. Pattison, L. R. Derogatis, and E. H. Uhlenhuth, "Length of Treatment with Anxiolytic Sedatives and Response to Their Sudden Withdrawal," Acta Psychiatr. Scand., 49, 51-64 (1973).
- [30] L. E. Hollister, "Withdrawal from Benzodiazepine Therapy," J. Am. Med. Assoc., 237, 1432 (1977).
- [31] D. K. Winstead, A. Anderson, M. K. Eilers, B. Blackwell, and A. L. Zaremba, "Diazepam on Demand: Drug-Seeking Behavior in Psychiatric Inpatients," Arch. Gen. Psychiatry, 30, 349-351 (1974).

- [32] B. Hubbard and D. F. Kripke, "Hypnotic and Minor Tranquilizer Use among Inpatients and after Discharge," Int. J. Addict., **11**, 403-408 (1976).
- [33] V. D. Patch, "The Dangers of Diazepam, a Street Drug," N. Engl. J. Med., **290**, 807 (1974).
- [34] G. E. Woody, J. Mintz, K. O'Hare, C. P. O'Brien, R. A. Greenstein, and E. Hargrove, "Diazepam Use by Patients in a Methadone Program—How Serious a Problem?" J. Psychodelic Drugs, **7**, 373-379 (1975).
- [35] K. Adam, L. Adamson, V. Brezinova, W. M. Hunter, and I. Oswald, "Nitrazepam: Lastingly Effective but Trouble on Withdrawal," Br. Med. J., **1**, 1558-1560 (1976).
- [36] D. J. Greenblatt, R. I. Shader, J. S. Harmatz, K. Franke, and J. Koch-Weser, "Absorption Rate, Blood Concentrations, and Early Responses to Oral Chlordiazepoxide," Am. J. Psychiatry, **134**, 559-562 (1977).
- [37] S. M. MacLeod, H. G. Giles, G. Patzalek, J. J. Thiessen, and E. M. Sellers, "Diazepam Actions and Plasma Concentrations Following Ethanol Ingestion," Eur. J. Clin. Pharmacol., **11**, 345-349 (1977).
- [38] A. Bliding, "Effects of Different Rates of Absorption of Two Benzodiazepins on Subjective and Objective Parameters," Ibid., **7**, 201-211 (1974).
- [39] L. Hillestad, T. Hansen, and H. Melsom, "Diazepam Metabolism in Normal Man. II. Serum Concentrations and Clinical Effect after Oral Administration and Cumulation," Clin. Pharmacol. Ther., **16**, 485-489 (1974).
- [40] S. A. Kaplan, M. L. Jack, K. Alexander, and R. E. Weinfeld, "Pharmacokinetic Profile of Diazepam in Man Following Single Intravenous and Oral and Chronic Oral Administration," J. Pharm. Sci., **62**, 1789-1796 (1973).
- [41] J. A. S. Gamble, J. W. Dundee, and R. C. Gray, "Plasma Diazepam Concentrations Following Prolonged Administration," Br. J. Anaesth., **48**, 1087-1090 (1976).
- [42] F. B. Eatman, W. A. Colburn, H. G. Boxenbaum, H. H. Posmanner, R. E. Weinfeld, R. Ronfeld, L. Weissman, J. D. Moore, M. Gibaldi, and S. A. Kaplan, "Pharmacokinetics of Diazepam Following Multiple-Dose Oral Administration to Healthy Human Subjects," J. Pharmacokinet. Biopharm., **5**, 481-494 (1977).

- [43] S. A. Kaplan, J. A. F. deSilva, M. L. Jack, K. Alexander, N. Strojny, R. E. Weinfeld, C. V. Puglisi, and L. Weissman, "Blood Level Profile in Man Following Chronic Oral Administration of Flurazepam Hydrochloride," J. Pharm. Sci., **62**, 1932-1935 (1973).
- [44] D. J. Greenblatt, R. I. Shader, and J. Koch-Weser, "Flurazepam Hydrochloride," Clin. Pharmacol. Ther., **17**, 1-14 (1975).
- [45] D. J. Greenblatt, R. I. Shader, and J. Koch-Weser, "Flurazepam Hydrochloride, A Benzodiazepine Hypnotic," Ann. Intern. Med., **83**, 237-241 (1975).
- [46] G. Cannizzaro, S. Nigito, P. M. Provenzano, and T. Vitikova, "Modification of Depressant and Disinhibitory Action of Flurazepam during Short Term Treatment in the Rat," Psychopharmacologia, **26**, 173-184 (1972).
- [47] L. Stein and B. D. Berger, "Psychopharmacology of 7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one (Lorazepam) in Squirrel Monkey and Rat," Arzneim.-Forsch., **21**, 1073-1078 (1971).
- [48] D. L. Margules and L. Stein, "Increase of Antianxiety Activity and Tolerance of Behavioral Depression during Chronic Administration of Oxazepam," Psychopharmacologia, **13**, 74-80 (1968).
- [49] K. Matsuki and T. Iwamoto, "Development of Tolerance to Tranquilizers in the Rat," Jpn. J. Pharmacol., **16**, 191-197 (1966).
- [50] D. J. Greenblatt and R. I. Shader, Benzodiazepines in Clinical Practice, Raven, New York, 1974, pp. 242-249.
- [51] E. S. Vesell, G. T. Passananti, J. P. Viau, J. E. Epps, and F. J. Di Carlo, "Effects of Chronic Prazepam Administration on Drug Metabolism in Man and Rat," Pharmacology, **7**, 197-206 (1972).
- [52] U. Klotz, K. H. Antonin, and P. R. Bieck, "Comparison of the Pharmacokinetics of Diazepam after Single and Subchronic Doses," Eur. J. Clin. Pharmacol., **10**, 121-126 (1976).
- [53] J. Kanto, E. Iisalo, V. Lehtinen, and J. Salminen, "The Concentrations of Diazepam and Its Metabolites in the Plasma after an Acute and Chronic Administration," Psychopharmacologia, **36**, 123-131 (1974).
- [54] R. Sellman, J. Kanto, E. Raijola, and A. Pekkarinen, "Induction Effect of Diazepam on Its Own Metabolism," Acta Pharmacol. Toxicol., **37**, 345-351 (1975).

- [55] Boston Collaborative Drug Surveillance Program, "Clinical Depression of the Central Nervous System Due to Diazepam and Chloriazepoxide in Relation to Cigarette Smoking and Age," N. Engl. J. Med., 288, 277-280 (1973).
- [56] U. Klotz, G. R. Avant, A. Hoyumpa, S. Schenker, and G. R. Wilkinson, "The Effects of Age and Liver Disease on the Disposition and Elimination of Diazepam in Adult Man," J. Clin. Invest., 55, 347-359 (1975).