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Dose-Response Studies on Tolerance to Multiple Doses of Secobarbital and Methaqualone in a Polydrug Abuse Population

THOMAS P. FAULKNER,* Ph.D., JAMES H. HAYDEN, M.D., Ph.D., CHANDER M. MEHTA, Ph.D., DONALD A. OLSON,† B.S., and ERIC G. COMSTOCK,‡ M.D.

School of Pharmacy
Texas Southern University

Institute of Clinical Toxicology
Houston, Texas 77030

ABSTRACT

Patients from a polydrug abuse treatment program were titrated with either secobarbital or methaqualone, their primary drug of abuse, to a state of mild intoxication, consisting of lateral and vertical nystagmus, ataxia, slurred speech, and drowsiness. The mean dose required to produce each sign was compared to that determined in a similarly treated control group. Tolerance to

*Present address: College of Pharmacy, Ohio Northern University, Ada, Ohio 45810.

†Present address: Smith Kline Laboratories, Houston, Texas 77036.

‡To whom requests for reprints should be addressed at Institute of Clinical Toxicology, 1802 Medical Towers, 1709 Dryden, Houston, Texas 77030.

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secobarbital was more easily demonstrated than tolerance to methaqualone, and nystagmus was the least sensitive indicator of patient tolerance. The individual signs were also cumulated into a graded rating scale of central nervous system depression which would be related to the dose administered. Tolerance was easily demonstrated at the higher stages of toxicity for secobarbital in the overall patient population, but tolerance to methaqualone was only unequivocal in the subjects indicating a relatively high frequency of abuse. Tolerance to methaqualone occurred at the lower stages of toxicity, suggesting that there is a difference between tolerance to secobarbital and tolerance to methaqualone. There was no indication that patients who also abuse alcohol are more tolerant than their patient counterparts. The patients who also had a history of amphetamine abuse, however, were less tolerant than the nonusers of these drugs.

INTRODUCTION

Secobarbital and methaqualone are sedative-hypnotics of the barbiturate and nonbarbiturate types, respectively. Both drugs have been abused for their effects on the central nervous system, and this abuse has been associated with both physical and psychological dependence [2, 3, 6, 7, 10, 11]. The repeated use of these drugs is also characterized by the need to progressively increase the dose to achieve the desired effects [1, 7, 10]. This effect provides the accepted definition for the term "tolerance."

Tolerance to the sedative effects of the barbiturates has been demonstrated in subjects given repeated doses of the drugs [1, 6, 9] and the dose requirements for the induction of tolerance by secobarbital has been determined [1]. There remains the need, however, for studies which quantitate the degree of tolerance existing in drug abusing subjects as a result of their own pattern of drug use.

Tolerance to secobarbital was investigated in a polydrug abuse population from an in-hospital treatment program [5]. These studies involved the titration of the patients to a mildly intoxicated state with secobarbital, their primary drug of abuse. In addition to a number of pharmacokinetic observations, it was determined that these subjects tolerated a total dose of secobarbital which was significantly higher than that tolerated by a similarly treated control group.

The following study is a reexamination of this study in terms of the individual determinants of toxicity. Similar data for methaqualone are examined for comparison. The objectives of the study were to relate the parameters to patient tolerance to the two drugs to examine the effects of the intensity and diversity of polydrug use to tolerance, and to develop a graded toxicity scale which could be related to the dose of the hypnotics.

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MATERIALS AND METHODS

Subjects

The experimental subjects in this study included 55 patients under treatment in an inpatient polydrug abuse clinic and a control group consisting of medical students and staff volunteers. The control subjects given secobarbital ranged in age from 17 to 31, and four of the subjects were female. The six control subjects given methaqualone included three females, and the age range was 22 to 31 years.

The patient population consisted of individuals who used sedative-hypnotics and considered either secobarbital or methaqualone as their primary drug of abuse. Some of the subjects used alcohol as well as drugs, but alcohol abuse was not considered the major drug problem. Likewise, a small minority of patients used narcotic analgesics sporadically, but were not considered physically or psychologically dependent on these drugs. The patients preferring secobarbital ranged in age from 16 to 29 years, and 12 of the 22 subjects were female. Fifteen of the 33 subjects preferring methaqualone were female, and the group ranged in age from 16 to 52 years.

Upon admission to the hospital, drug histories were taken and blood and urine samples were collected in order to screen for methaqualone, barbiturates, and other common drugs of abuse. Patients reporting the use of three or more therapeutic doses per day of a sedative-hypnotic for the previous 3 months were considered to be in a "high frequency" group compared to the remainder of the population. Similarly, patients who indicated the use of over 8 ounces of alcohol per day were considered to be among an "alcohol abusing" group, and patients reporting any degree of amphetamine use were among the "amphetamine abusing" group. The detection of barbiturates in either the blood or urine of the patients preferring secobarbital placed the subject in a "positive screen group." The detection of either barbiturates or methaqualone in the samples from patients preferring methaqualone placed the subject in the "positive screen group." This subgroup eliminates patients known not to be physically dependent on sedative-hypnotics, and thus less apt to be tolerant to the drugs.

Titration Procedure

The titration procedure was employed clinically in order to determine an appropriate maintenance and withdrawal schedule for detoxification. The general procedure used by this clinic has been previously reported [8]. Each subject was given either secobarbital sodium (Seconal sodium, Eli Lilly & Co., 100 to 200 mg/hr, p.o.) or methaqualone (Quaalude, W. H. Rorer, 300 to 600 mg/hr, p.o.) until signs of mild intoxication occurred.

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Staff nurses and paramedical personnel were specially trained to recognize the onset of toxicity signs, and monitored the patient throughout the titration procedure. Observations were made immediately preceding each dose administration and consisted of the following: (1) vertical nystagmus—oscillation of the eyeballs upon vertical gaze, (2) lateral nystagmus—oscillation of the eyeballs upon lateral gaze, (3) ataxia—inability to walk without assistance, (4) slurred speech—difficulty in articulation of short sentences, and (5) drowsiness—nods in the absence of stimulation. The titration procedure was terminated when either all signs had been determined or the severity of intoxication required discontinuation of the procedure.

The patients who indicated secobarbital as their primary drug of abuse were titrated with secobarbital and those indicating methaqualone as the primary agent were titrated with this drug. Two separate control groups were also titrated with either secobarbital or methaqualone. The procedure began at approximately 9:00 a.m. on the day following patient admission, and all subjects were fasted the previous 12 hr.

Treatment of Data

The total dose administered before the onset of each sign was recorded and normalized per 150 lb of body weight. The mean logarithmic dose required to produce each sign was calculated for the control groups, total patient groups, and each subgroup described above. Patients failing to demonstrate an individual sign before the termination of titration were excluded from that group. The mean dose and 95% confidence limits were calculated from these data. Intergroup statistical comparisons were made using Student's "t" test and the logarithmic values of the mean and standard error of the mean.

The stages of toxicity were defined in terms of the number of the individual signs which were observed following a given dose. Thus a subject demonstrating any one of the signs was considered to have manifested Stage 1; any two signs, Stage 2; etc. Subjects demonstrating sufficient toxicity to require termination of the titration procedure were considered to have demonstrated an additional sign in the cumulative rating scale. When multiple signs developed after a given dose, the subject was considered to have reached all previous stages, as well as the stage in question.

The total dose required to produce each stage was normalized for body weight, and the mean values for each group were calculated as described for the individual signs.

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RESULTS

It should initially be emphasized that the majority of the patients has received or taken doses of sedative-hypnotics as recently as 10 hr before the beginning of the titration procedure. This situation resulted from either self-administration of drugs before admission or the necessity for maintenance doses in the potentially dependent patients. The dose tolerated by the patients should therefore be considered an underestimation of the dose which might be tolerated in the "drug-free" state.

Figure 1 shows the mean dose values required to produce each toxicity sign in the patient and control groups titrated with either secobarbital or methaqualone. These values are also shown for two patient subgroups, one limited to those patients presenting with a positive admission screen and another limited to patients indicating a high frequency of sedative-hypnotic abuse. The mean dose of secobarbital required to produce ataxia and drowsiness in the total patient population was significantly greater than that required to produce these symptoms in the control group. There is a similar trend in the dose required to produce slurred speech, but the difference is not significant. The mean dose required to produce either vertical or lateral nystagmus was nearly identical between the two groups. Limiting these observations to the "positive screen" or "high frequency" groups did not provide additional information.

There were no significant differences in any toxicity sign between the control group and the overall patient group titrated with methaqualone. If these observations are limited to the "positive screen" group, it may be seen that the mean dose required to produce ataxia in these patients is significantly greater than the control value. Likewise, the mean doses of methaqualone required to produce ataxia and slurred speech in the "high frequency" group were significantly greater than the corresponding doses in the control group. These values, and the mean dose required to produce lateral nystagmus in this group, are also significantly greater than the corresponding mean doses required to produce these signs in the patients, indicating a lower frequency of abuse (i.e., patient countergroup).

The log dose-response curves resulting from the calculation of the mean dose required to produce each stage of toxicity are shown in Fig. 2. The doses of secobarbital required to produce Stages 3, 4, and 5 in the patient population are significantly greater than the control values. These values for the lower stages are, however, nearly identical between groups. The only difference between the patients titrated with methaqualone and the corresponding control group was the significantly greater dose required to produce Stage 3 in the patient group.

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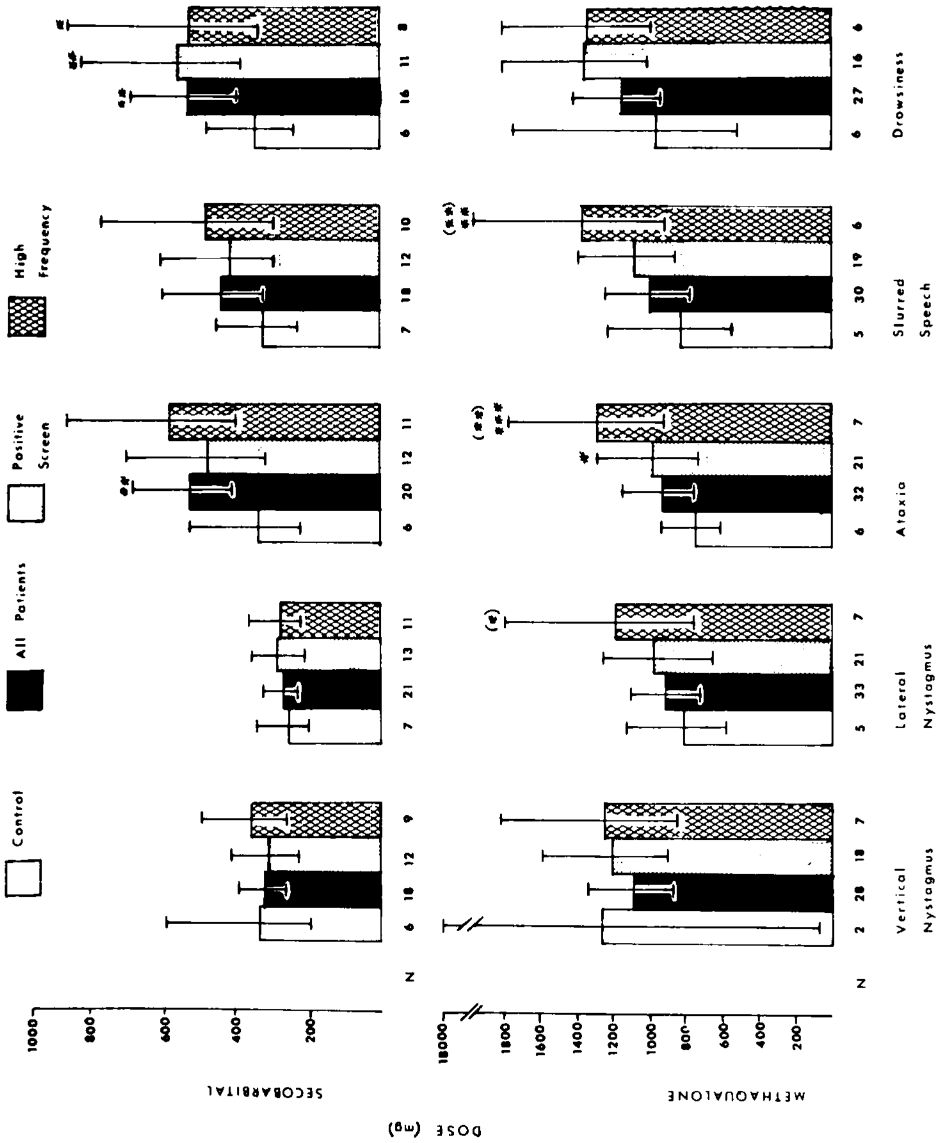

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FIG. 1. Toxicity signs in polydrug abusing patients and control subjects titrated with secobarbital or methaqualone. Each bar represents the mean dose required to produce each sign for the group in question. The brackets are 95% confidence limits. The number of subjects responding with each sign is shown beneath each bar. Significance levels: $^{*}p < 0.05$ vs control; $^{**}p < 0.025$ vs control; $^{***}p < 0.005$ vs control; $(^{*})p < 0.05$ vs patient countergroup; $(^{**})p < 0.025$ vs patient countergroup.

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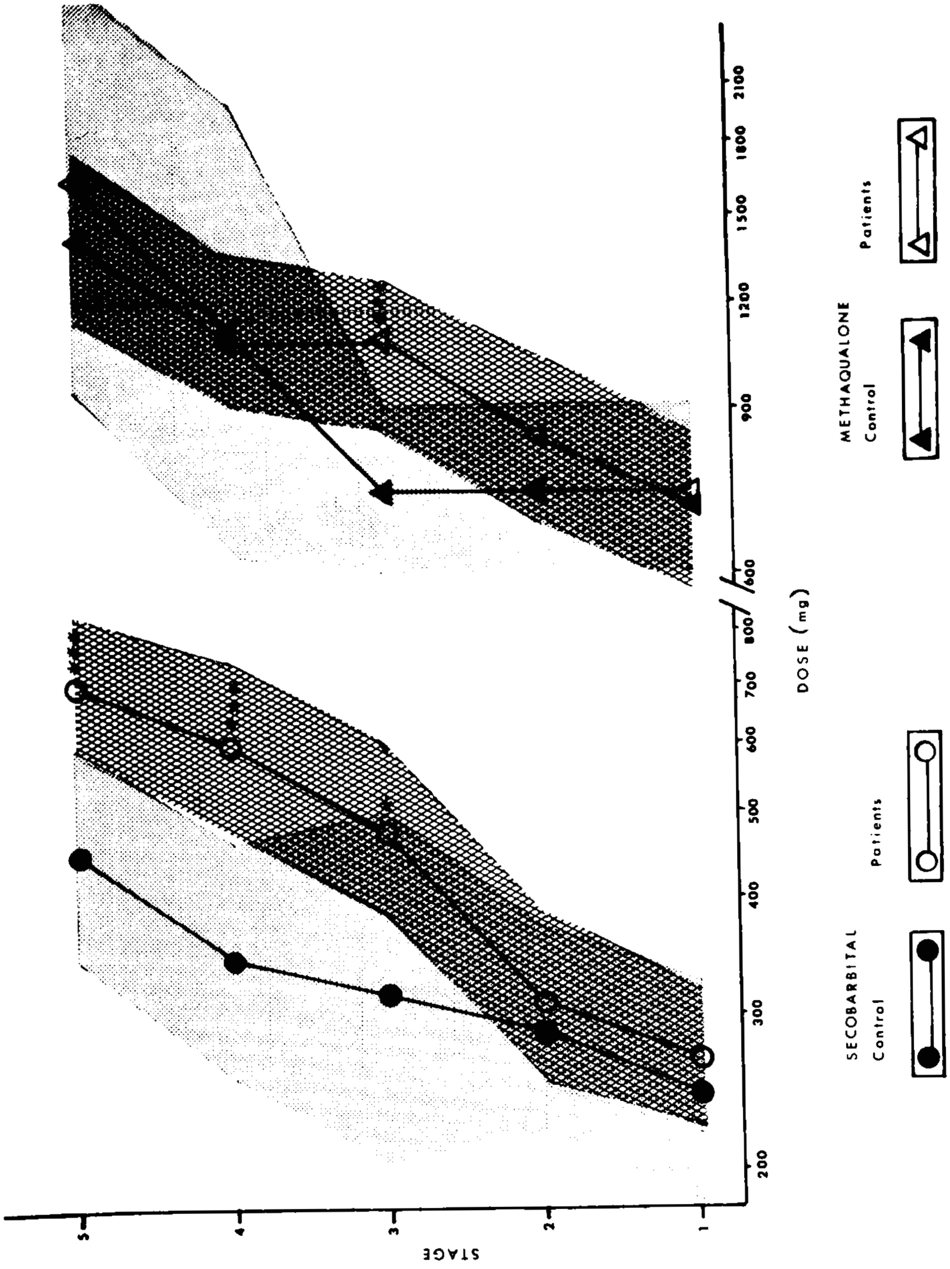

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FIG. 2. Dose-response curves for the stages of toxicity in polydrug abusing patients and control subjects titrated with secobarbital or methaqualone. Each point represents the mean dose required to produce each stage for the group in question. The shaded areas represent 95% confidence limits. The number of patients in each group reaching Stages 1, 2, 3, 4, and 5 were, respectively: secobarbital control group, 7, 7, 7, 6, and 5; secobarbital patient group, 22, 22, 22, 21, and 21; methaqualone control group, 6, 6, 6, 6, and 5; methaqualone patient group, 33, 33, 32, 30, and 25. Significance levels: $^*p < 0.05$ vs control; $^{***}p < 0.005$ vs control.

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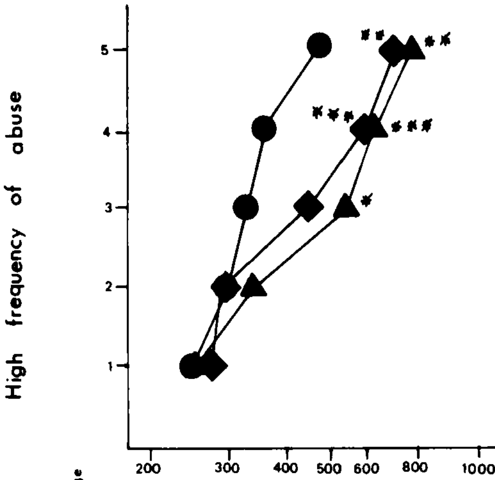
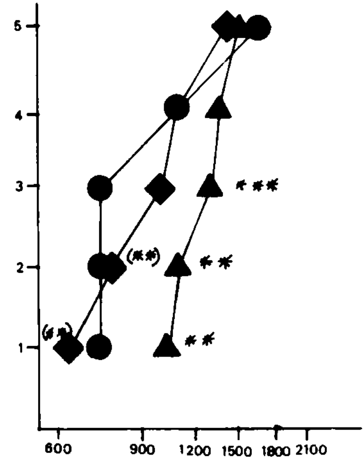
Secobarbital

Methaqualone

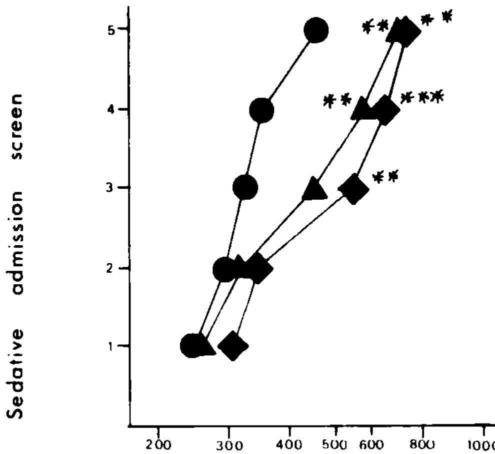
High frequency of abuse

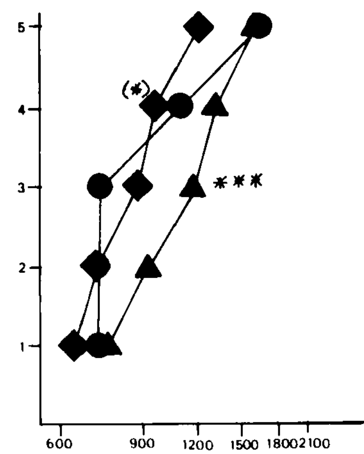
Stage





Sedative admission screen

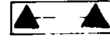




Dose (mg)

Control

Negative


Positive

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A comparison between the secobarbital and methaqualone control groups indicates that the relative doses required to produce each stage are equivalent to their respective therapeutic doses (100 mg secobarbital vs 300 mg methaqualone).

Figure 3 shows the dose-response curves which result after dividing the patient populations on the basis of their admission screens or alleged frequency of sedative-hypnotic abuse. The control values are reproduced for comparison. Within the patient population titrated with secobarbital, these subgroups do not differ from their patient counterparts. Separating the patient population titrated with methaqualone on the basis of frequency of abuse does produce significant results. The doses required to produce Stages 1, 2, and 3 in the "high frequency" group differed significantly from the control values, and the dose required to produce Stages 1 and 2 in this group also differed significantly from the low frequency countergroup. There is a similar trend when these observations are limited to the "positive screen group," but the only significant differences occurred between this group vs the countergroup at Stage 4, and vs the control group at Stage 3.

The dose-response curves for the patient populations divided on the basis of their alcohol and amphetamine use are shown in Fig. 4. The only significant difference between the patients indicating a greater degree of alcohol use and the remainder of the population was seen at Stage 1 in the group titrated with methaqualone. The "alcohol-abusing" group tolerated a dose of methaqualone to reach this stage which was significantly greater than that tolerated by the countergroup.

Greater differences were evident within the patient population when

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FIG. 3. Dose-response curves for control subjects and patients grouped on the basis of their alleged frequency of abuse and their admission drug screens. Each point represents the mean dose required to produce each stage for the group in question. The number of patients in each group reaching Stages 1, 2, 3, 4, and 5 were, respectively: secobarbital, high frequency, 11, 11, 11, 11, and 11; secobarbital, low frequency, 11, 11, 11, 10, and 10; secobarbital, positive admission screen, 14, 14, 14, 13, and 13; secobarbital, negative admission screen, 8, 8, 8, 8, and 8; methaqualone, high frequency, 8, 8, 7, 6, and 5; methaqualone, low frequency, 25, 25, 25, 24, and 20; methaqualone, positive, admission screen, 22, 22, 21, 19, and 16; methaqualone, negative admission screen, 11, 11, 11, 11, and 9. Significance levels: *$p < 0.05$ vs control; **$p < 0.025$ vs control; ***$p < 0.005$ vs control; (*)$p < 0.05$ vs countergroup; (**)$p < 0.025$ vs patient countergroup.

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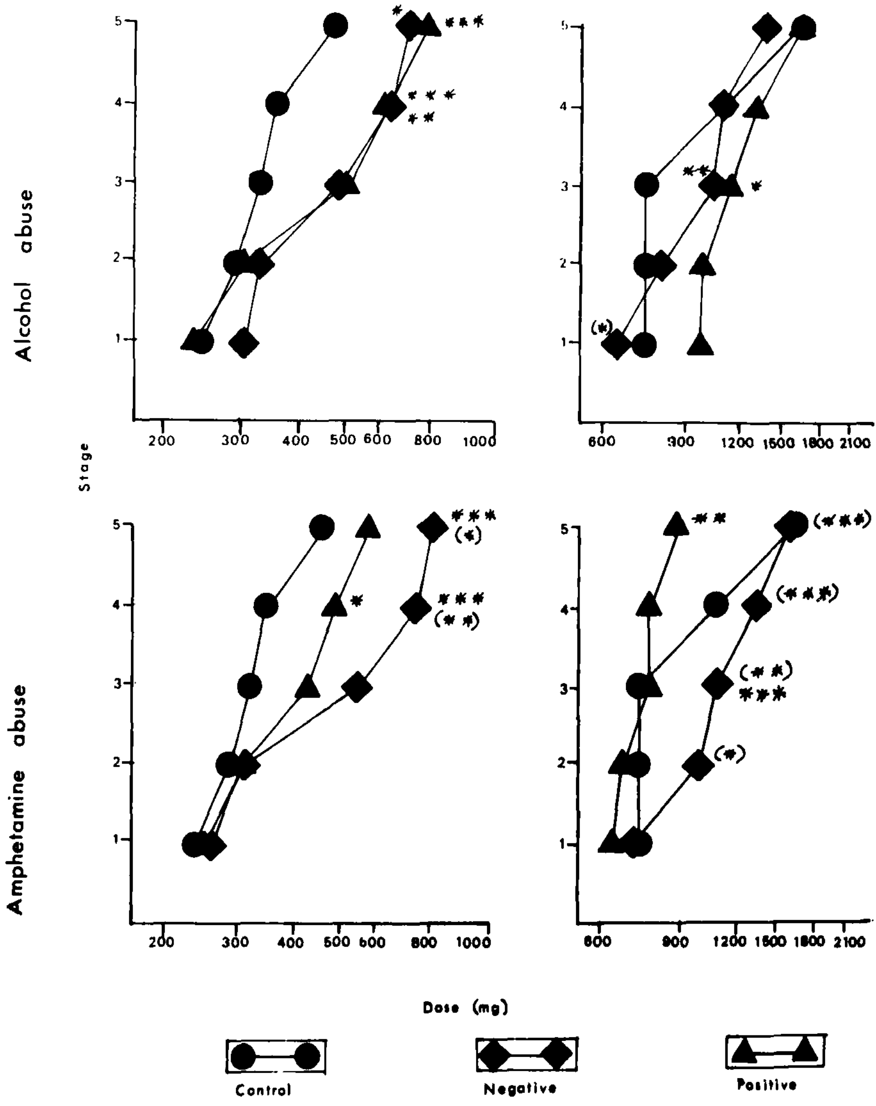

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amphetamine use was considered. In the patient population titrated with secobarbital, the dose required to produce both Stages 4 and 5 was significantly less in the amphetamine-using subgroup than in the balance of the population. It should be noted that if only the amphetamine-abusing subjects were considered, the subjects would only differ from the control group at Stage 4. Similarly, the doses of methaqualone required to produce Stages 2, 3, 4, and 5 were significantly less for the amphetamine-using subjects than for their patient counterparts. The mean dose of methaqualone required to produce Stage 5 in the amphetamine-abusing population was also significantly less than the corresponding dose in the control subjects.

DISCUSSION

There was no apparent pattern in the order of appearance of the various signs of toxicity in either of the control populations. The mean dose producing each sign was on the order of three hypnotic doses. Ewing and Bakewell [4] report that 200 mg of pentobarbital produces drowsiness, slurred speech, and coarse nystagmus in drug-abusing subjects using 500 to 600 mg/day of barbiturate. Considerably higher doses of secobarbital and, in therapeutic equivalents, methaqualone were required to produce these signs in both the patients and control group.

It is interesting that vertical and lateral nystagmus were the least sensitive end points in the detection of tolerance. Indeed, it is questionable whether tolerance to nystagmus occurs in this population.

FIG. 4. Dose-response curves for control subjects and patients grouped according to alcohol and amphetamine use. Each point represents the mean dose required to produce each stage for the group in question. The number of patients in each group reaching Stages 1, 2, 3, 4, and 5 were, respectively: secobarbital, alcohol abusers, 12, 12, 12, 12, and 12; secobarbital, nonalcohol abusers, 10, 10, 10, 9, and 9; secobarbital, amphetamine abusers, 11, 11, 11, 11, and 11; secobarbital, nonamphetamine abusers, 11, 11, 11, 10, and 10; methaqualone, alcohol abusers, 8, 8, 8, 8, and 6; methaqualone, nonalchhol abusers, 25, 25, 24, 22, and 19; methaqualone, amphetamine abusers 9, 9, 9, 9, and 6; methaqualone, nonamphetamine abusers 24, 24, 23, 21, and 19. Significance levels: *p $<$ 0.05 vs control; **p $<$ 0.025 vs control; ***p $<$ 0.005 vs control; (*)p $<$ 0.05 vs countergroup; (**)p $<$ 0.025 vs patient countergroup; (***)p $<$ 0.005 vs patient countergroup.

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The rating scale proved more effective than the individual signs in quantitating the depressant effects of the drugs and in differentiating the polydrug abuse population from the control subjects. The data indicate that the average, pharmacologically naive individual will develop one or two of the signs after two or three therapeutic doses and develop the entire syndrome after five or six doses.

Tolerance to secobarbital was easily demonstrated in the total patient population titrated with this drug. The polydrug abuse subjects tolerated approximately twice the dose required by the control subjects to reach the upper stages of toxicity. Tolerance to methaqualone in the patient group was only apparent at Stage 3, but none of the individual signs had been sufficiently sensitive to demonstrate tolerance to this drug in the overall population. Tolerance to methaqualone was more apparent in the patient sample limited to subjects indicating a relatively high frequency of sedative-hypnotic abuse.

The shape of the dose-response curves in the high frequency sedative-hypnotic abusers (Fig. 3) suggests that there is a difference between tolerance to secobarbital and tolerance to methaqualone. Tolerance to methaqualone is evident at the lower stages of toxicity whereas tolerance to secobarbital is seen at the higher stages. It should be noted that tolerance to the total dose of methaqualone (Stage 5) cannot be demonstrated.

It should be reemphasized that the patients were titrated with their primary drug of abuse. Therefore, there could be a difference in the adaptive changes produced by repeated use of the two drugs. Evidence has been presented that methaqualone is a less potent inducer of drug-metabolizing enzymes [13].

Although alcoholics have been shown to be more tolerant to several hypnotics and sedatives [12], there is little evidence that the amount of alcohol use described here affects the response to either drug. On the other hand, amphetamine-abusing subjects were considerably less tolerant than their patient counterparts. Indeed, the amphetamine-abusing subjects are even more sensitive than the control subjects at Stage 5. The possibility that amphetamine-abusing subjects have a lesser actual degree of involvement with sedative-hypnotics has been discussed [5]. The possibility of a pharmacological interaction also exists and warrants further investigation.

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