Pharmacology Biochemistry and Behavior, Vol. 41, pp. 355–360, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Rapid Tolerance and Cross-Tolerance as Predictors of Chronic Tolerance and Cross-Tolerance

J. M. KHANNA,[1] H. KALANT, J. WEINER AND G. SHAH

Department of Pharmacology, University of Toronto, Toronto, Canada M5S 1A8
Addiction Research Foundation of Ontario, Toronto, Canada M5S 2S1

Received 1 April 1991

KHANNA, J. M., H. KALANT, J. WEINER AND G. SHAH. *Rapid tolerance and cross-tolerance as predictors of chronic tolerance and cross-tolerance.* PHARMACOL BIOCHEM BEHAV **41**(2) 355–360, 1992.—Hypothermia and motor impairment (tilt-plane) tests were used to assess the phenomenona of rapid tolerance to ethanol and cross-tolerance to various alcohols, benzodiazepines, and barbiturates that differ in lipid:water partition coefficients. The hypothermic and motor impairment responses to ethanol were significantly reduced on day 2 in rats receiving ethanol (2 doses of 2 g/kg each for the hypothermia test and 2.3 and 1.7 g/kg for the tilt-plane test) 24 and 22 h earlier compared to the control group pretreated with saline. Ethanol pretreatment resulted in rapid cross-tolerance, on both tests, to the various alcohols (*n*-propanol, *n*-butanol, and *t*-butanol) and the benzodiazepines (chlordiazepoxide, diazepam, oxazepam, and flurazepam) tested. Ethanol pretreatment also conferred clear rapid cross-tolerance to barbital and phenobarbital, but did not result in rapid cross-tolerance to pentobarbital, secobarbital, amobarbital, or thiopental. The results on rapid cross-tolerance on both tests seen in these studies parallel the results obtained in chronic tolerance and cross-tolerance studies reported recently. These results suggest that rapid tolerance and cross-tolerance can be used as predictors of chronic tolerance and cross-tolerance.

Rapid tolerance Cross-tolerance Alcohols Barbiturates Benzodiazepines Rat

IN recent work (11,12), we used a model similar to that described by Crabbe et al. (5) to investigate rapid tolerance to ethanol and pentobarbital and cross-tolerance between them. The hypothermic and motor-impairment responses to ethanol were significantly reduced on day 2 in animals that had received ethanol (2 doses of 2 g/kg each) 24 and 22 h earlier compared to the control group pretreated with saline. Ethanol pretreatment, however, did not result in rapid cross-tolerance to pentobarbital in either test. In other studies, pentobarbital pretreatment 24 h earlier resulted in rapid tolerance to pentobarbital and also conferred rapid cross-tolerance to ethanol. This asymmetry of rapid cross-tolerance between ethanol and pentobarbital matches the asymmetry observed by us and others in chronic tolerance and cross-tolerance studies reported earlier (3,8,13). The findings suggest that rapid tolerance and cross-tolerance can be used as predictors of chronic tolerance and cross-tolerance.

These present studies were undertaken to examine rapid cross-tolerance to various alcohols, barbiturates, and benzodiazepines to test further the validity of the rapid tolerance model as a predictor of chronic tolerance.

METHOD

Animals

Male Sprague-Dawley rats were obtained from Charles River Canada (Montreal, Quebec) at initial body weights of 150–200 g. They were housed singly in a colony room maintained at 21 ± 1°C with lights on from 7 a.m. to 7 p.m. Tapwater was available at all times. Purina Rat Chow was given ad lib until body weights reached 200–250 g. Thereafter, the daily ration was restricted and individually adjusted to maintain comparable body weights in the various groups to ensure comparable baseline (predrug) performance on the tilt-plane test.

Test Procedures

Hypothermia. A 5-cm thermistor probe was inserted in the rectum and left until a stable temperature recording was obtained (approximately 30 s) on a Yellow Springs Instrument electrical thermometer. This was done before, and at successive 30-min intervals after, the intraperitoneal test injection

[1] Requests for reprints should be addressed to Dr. J. Khanna, Department of Pharmacology, Medical Sciences Building, University of Toronto, Toronto, Ontario, Canada, M5S 1A8.

until the temperature began to return to normal. This generally occurred about 60–90 min after injection of all drugs except *n*-propanol and *n*-butanol, with which the peak occurred earlier (30 min). The hypothermic effect was quantified as the maximum drop in temperature regardless of the time of its occurrence.

Motor impairment. The tilting-plane test was used as a measure of motor impairment (1,8). The apparatus consists of a flat board that can be inclined at a fixed angular velocity through a range of 55° above the horizontal. The animal is placed on the slightly roughened surface of the board, which is then tilted until the animal begins to slide from the starting position. The test measure is the angle at which this occurs. The sliding angle was measured before and at 30, 60, and 90 min after injection of the drug. The degree of postdrug ataxia was expressed as the percentage change in the sliding angle compared to the same animal's predrug value. Maximum ataxia, regardless of the time of its occurrence, was employed as the measure of drug effect. This generally occurred about 30 min after injection in all cases except for *n*-propanol and *n*-butanol, which produced peak impairment at 15 min.

Rapid Tolerance to Ethanol and Cross-Tolerance to Different Alcohols, Barbiturates, and Benzodiazepines (Hypothermia Test)

Two groups of rats (n = 24 per group) were used for the hypothermia studies. On day 1 of each test period, half the first group received IP ethanol (2.0 g/kg) and the other half was injected with IP saline. Before and at 30, 60, 90, and 120 min after ethanol or saline injections, rectal temperature was measured. Immediately after the last temperature measurement, rats received a second dose of ethanol (2.0 g/kg IP) or saline, respectively, and were then returned to their home cages. On day 2, an identical procedure was followed except all animals received ethanol (2.0 g/kg IP) before the temperature measurement. The animals were then left in their home cages for a period of at least 10 days without drug administration or testing to allow them to return to baseline before the succeeding test periods that were used for studying rapid cross-tolerance to various barbiturates. On day 1 of each period, rats were again randomly reassigned to ethanol and saline treatment groups as described above. On day 2 of each period, all rats were tested under the particular barbiturate being examined. The second group of 24 rats was used for studying rapid cross-tolerance to various alcohols and benzodiazepines in a design exactly comparable to that used for the first group. The sequence of drugs tested and the length of the intervening recovery intervals are shown in Table 1.

Doses used for the various drugs were selected to give responses in the middle portion of the dose-response curve as determined in previous studies in this laboratory. Rapid tolerance to ethanol in both groups was examined three times: 1) before the start of cross-tolerance studies, 2) halfway through the cross-tolerance testing, and 3) at the end of the cross-tolerance studies. Rapid tolerance to ethanol was essentially similar at all three times.

Rapid Tolerance to Ethanol and Cross-Tolerance to Various Alcohols, Barbiturates, and Benzodiazepines (Tilt-Plane Test)

For these studies, four separate groups of rats (n = 24 per group) were again employed in a design similar to that described above. Ethanol (2.3 g/kg) or saline was given IP on day 1 of each test period. This dose was used, rather than 2.0 g/kg, to produce an effect in the midrange of the dose-response curve for the tilt-plane test. After the last tilt-plane test on day 1, a second dose of ethanol (1.7 g/kg) or saline was then given IP; the second dose of ethanol provided the same total dose of ethanol (4 g/kg) as in the hypothermia study.

TABLE 1

SEQUENCE OF DRUG TESTING AND [RECOVERY INTERVALS] FOR RAPID TOLERANCE AND RAPID CROSS-TOLERANCE STUDIES

Hypothermia studies
- Group 1: ethanol-[2 wk]-pentobarbital-[10 days]-barbital-[4 wk]-thiopental-[2 wk]-secobarbital-[10 days]-amobarbital-[10 days]-phenobarbital
- Group 2: ethanol-[10 days]-*n*-butanol-[10 days]-*n*-propanol-[2 wk]-*t*-butanol-[10 days]-diazepam-[2 wk]-flurazepam-[2 wk]-oxazepam-[3 wk]-chlordiazepoxide.

Tilt-plane studies
- Group 1: ethanol-[2 wk]-thiopental-[1 wk]-amobarbital-[1 wk]-pentobarbital-[1 wk]-secobarbital
- Group 2: *n*-butanol-[1 wk]-chlordiazepoxide-[2 wk]-oxazepam
- Group 3: *t*-butanol-[1 wk]-flurazepam-[2 wk]-barbital
- Group 4: *n*-propanol-[2 wk]-diazepam-[2 wk]-phenobarbital

On day 2, ethanol (2.3 g/kg) was administered IP to animals being tested for rapid tolerance to ethanol. In studies on cross-tolerance, ethanol or saline was given on day 1 and the various other drugs were used on day 2. The sequence of drugs used for each group, and the lengths of intervening recovery intervals, are shown in Table 1.

Statistical analysis. All time course data were subjected to analysis of variance (ANOVA) for the main effect of treatment and time of measurements using the statistical package BMDP-2V. Group means of treated and untreated groups taken on single test days were compared by means of Student's two-tailed t-test for unpaired data.

RESULTS

Hypothermia

Cross-tolerance between ethanol and other alcohols. Rats treated with ethanol on day 1 showed a significantly smaller hypothermia response to ethanol on day 2 than those that had received saline on day 1 (t = 3.294, df = 22, $p < 0.01$). Cross-tolerance to other alcohols was also significant on day 2 (Fig. 1): for *n*-butanol (0.36 g/kg), t = 2.219, df = 22, $p < 0.05$; *n*-propanol (0.9 g/kg), t = 2.639, df = 22, $p < 0.02$; and *t*-butanol (0.55 g/kg), t = 3.375, df = 22, $p < 0.01$.

Cross-tolerance between ethanol and benzodiazepines. Rats pretreated with ethanol showed significantly smaller responses to the hypothermic effects of different benzodiazepines on day 2 than saline-pretreated rats (Fig. 1). This indicates rapid development of cross-tolerance to these benzodiazepines. For chlordiazepoxide (14 mg/kg), t = 2.289, df = 22, $p < 0.05$; flurazepam (30 mg/kg), t = 3.299, df = 22, $p < 0.01$; diazepam (6.5 mg/kg), t = 2.647, df = 22, $p < 0.02$; and oxazepam (20 mg/kg), t = 2.939, df = 22, $p < 0.01$.

Cross-tolerance between ethanol and barbiturates. The results of this experiment are shown in Fig. 2. Rats injected with ethanol or saline on day 1 were tested for cross-tolerance to the hypothermic effect of different barbiturates on day 2.

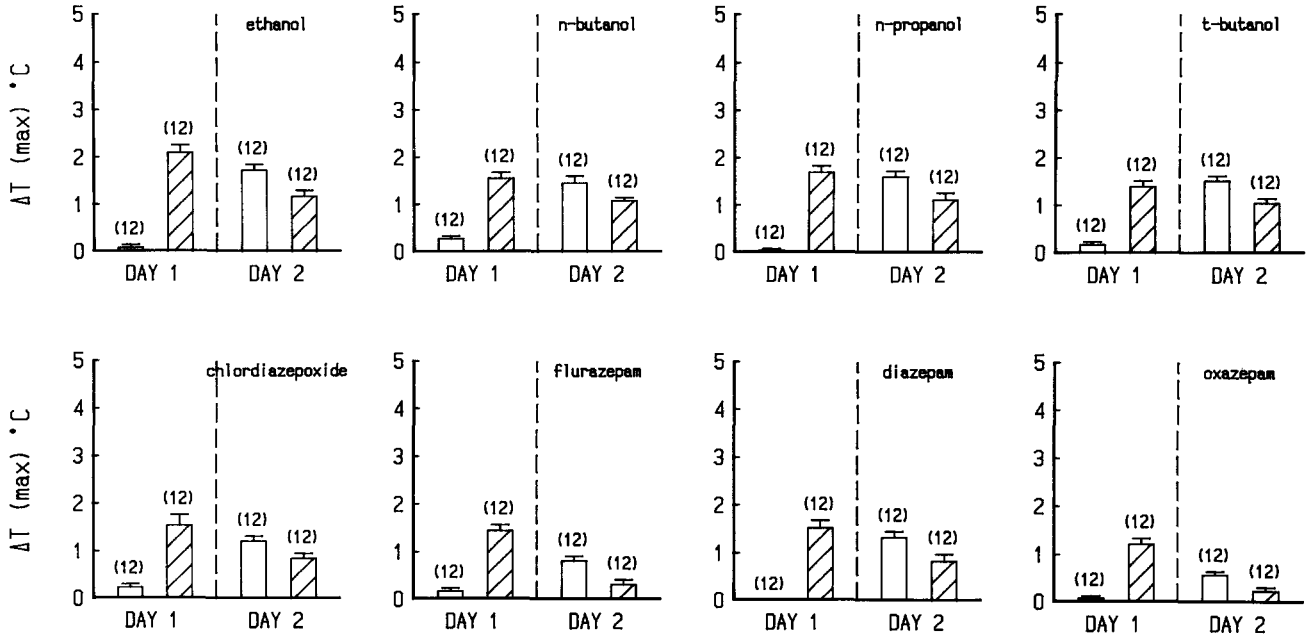

FIG. 1. Maximum hypothermic response (ΔT_{max}°C) in rats given on day 1 saline (open bars) or ethanol (two doses of 2 g/kg IP, 2 h apart; hatched bars). On day 2, both groups were injected with IP ethanol (2.0 g/kg), *n*-butanol (0.36 g/kg), *n*-propanol (0.9 g/kg), *t*-butanol (0.55 g/kg), chlordiazepoxide (14 mg/kg), flurazepam (30 mg/kg), diazepam (6.5 mg/kg), or oxazepam (20 mg/kg). The *test drug* is shown at the top of the corresponding day 2 panel; the same symbols (open or hatched bars) represent the respective pretreatment groups from day 1. Vertical lines indicate positive half of the standard error, with number of animals per group shown in parentheses above the bars.

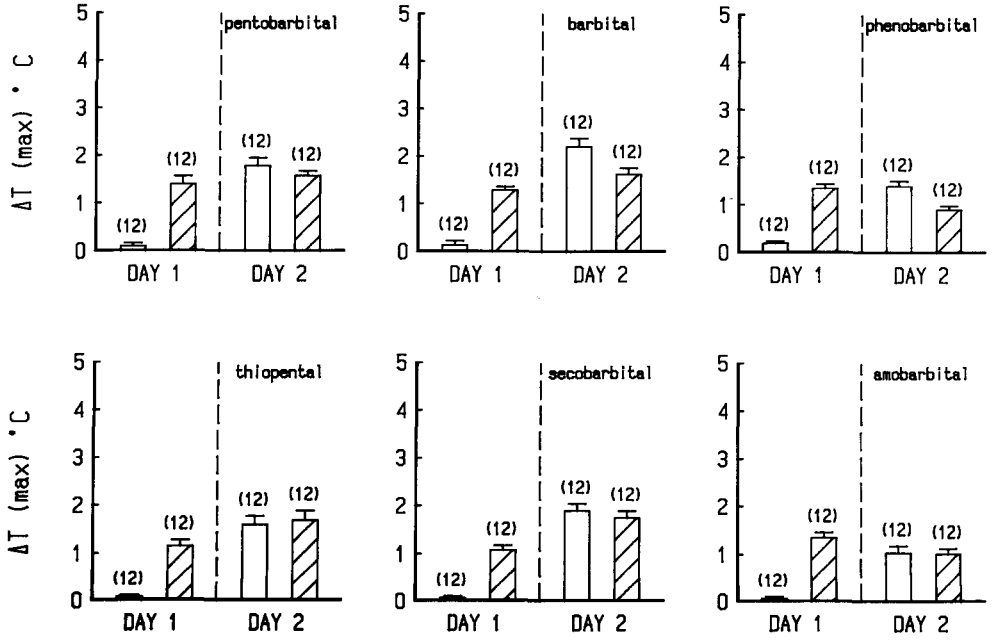

FIG. 2. Maximum hypothermic response in rats given saline or ethanol on day 1 as described in Fig. 1. On day 2, both groups were injected IP with pentobarbital (20 mg/kg), barbital (105 mg/kg), phenobarbital (55 mg/kg), thiopental (28 mg/kg), secobarbital (22 mg/kg), or amobarbital (30 mg/kg). Drug labeling at the top of the figures, symbols, and error bars are as described in Fig. 1.

Cross-tolerance is seen to barbital (105 mg/kg), $t = 2.596$, $df = 22$, $p < 0.02$, and phenobarbital (55 mg/kg), $t = 3.553$, $p < 0.01$.

There was no rapid cross-tolerance to the other barbiturates tested: Rats pretreated with ethanol or saline showed nearly identical responses to the hypothermic effects of these barbiturates. For pentobarbital (20 mg/kg), $t = 1.068$, $df = 22$, $p > 0.30$; thiopental (28 mg/kg), $t = 0.305$, $df = 22$, $p > 0.98$; secobarbital (22 mg/kg), $t = 0.688$, $df = 22$, $p > 0.50$; and amobarbital (30 mg/kg), $t = 0.108$, $df = 22$, $p > 0.95$.

Motor Impairment

Cross-tolerance between ethanol and other alcohols. Rapid development of tolerance to the motor-impairment effect of ethanol on day 2 was clearly seen in rats that received ethanol on day 1 ($t = 3.569$, $df = 24$, $p < 0.005$). Cross-tolerance to other alcohols was also significant on day 2 (Fig. 3). For *n*-butanol (0.49 g/kg), $t = 2.683$, $df = 16$, $p < 0.02$; *n*-propanol (1.0 g/kg), $t = 2.802$, $df = 16$, $p < 0.02$; and *t*-butanol (0.7 g/kg), $t = 2.742$, $df = 14$, $p < 0.05$.

Cross-tolerance between ethanol and benzodiazepines. Rats injected with ethanol on day 1 showed a significant development of rapid cross-tolerance to the motor-impairing effect of benzodiazepines on day 2; for chlordiazepoxide (16 mg/kg), $t = 3.321$, $df = 18$, $p < 0.005$; flurazepam (25 mg/kg), $t = 6.192$, $df = 18$, $p < 0.001$; diazepam (6 mg/kg), $t = 2.738$, $df = 18$, $p < 0.02$; and oxazepam (20 mg/kg), $t = 5.407$, $df = 17$, $p < 0.001$.

Cross-tolerance between ethanol and barbiturates. The results of this experiment are illustrated in Fig. 4. Rats injected with ethanol or saline on day 1 showed significant cross-tolerance on day 2 to barbital (120 mg/kg), $t = 4.663$, $df = 18$, $p < 0.001$, and phenobarbital (75 mg/kg), $t = 3.81$, $df = 18$, $p < 0.005$. There was no rapid cross-tolerance to the other barbiturates: for pentobarbital (23 mg/kg), $t = 1.53$, $df = 18$, $p > 0.20$; thiopental (25 mg/kg), $t = 1.304$, $df = 22$, $p > 0.31$; amobarbital (28 mg/kg), $t = 0.344$, $df = 22$, $p > 0.90$; and secobarbital (16 mg/kg), $t = 0.867$, $df = 21$, $p > 0.40$. The maximum percentage impairment values with all these four barbiturates were somewhat lower on day 2 in ethanol-pretreated than in saline-pretreated animals. However, a two-way ANOVA (pretreatment, drug) with repeated measures (times) for comparison of area under the curve (i.e., over all time points) on day 2 for ethanol vs. saline groups was also not significant.

DISCUSSION

Recently, we compared results on rapid cross-tolerance between ethanol and pentobarbital (11,12) with results obtained in studies using a chronic model of cross-tolerance (8,14). The similarity between results on rapid tolerance and those on chronic tolerance suggested that rapid tolerance may be a predictor for chronic tolerance. It remained to be determined whether other barbiturates, or drugs such as other alcohols and benzodiazepines, also yield similar results in studies of rapid cross-tolerance and chronic cross-tolerance.

The results of this study provide clear evidence of rapid cross-tolerance between ethanol and various other alcohols, as well as between ethanol and benzodiazepines. It could be argued that the experimental design, involving repeated tests on the same animals, confounds the interpretation by carry-over effects from one test to the next so the later test results could not be taken as true measures of rapid tolerance. However, intervals of 1–4 weeks between tests were intended to allow the animals to return to initial levels of drug sensitivity before each test period, and they evidently succeeded in doing so. Thus, day 1 test results with ethanol in each group of

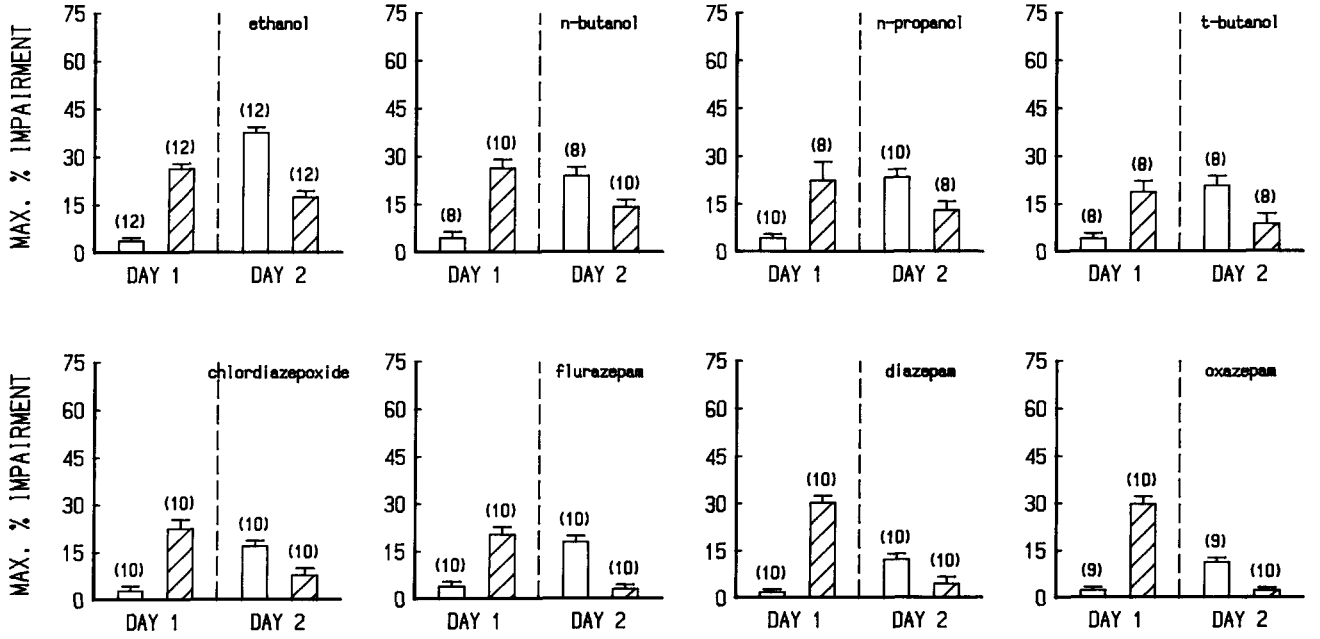

FIG. 3. Maximum percentage impairment (tilt-plane test) in rats given on day 1 saline (open bars) or ethanol (two doses of 2.3 and 1.7 g/kg IP, 2 h apart; hatched bars). On day 2, both groups were injected IP with ethanol (2.3 g/kg), *n*-butanol (0.49 g/kg), *n*-propanol (1.0 g/kg), *t*-butanol (0.7 g/kg), chlordiazepoxide (10 mg/kg), flurazepam (25 mg/kg), diazepam (6 mg/kg), or oxazepam (20 mg/kg). Drug labeling at top of the figures, symbols, and error bars are as described in Fig. 1.

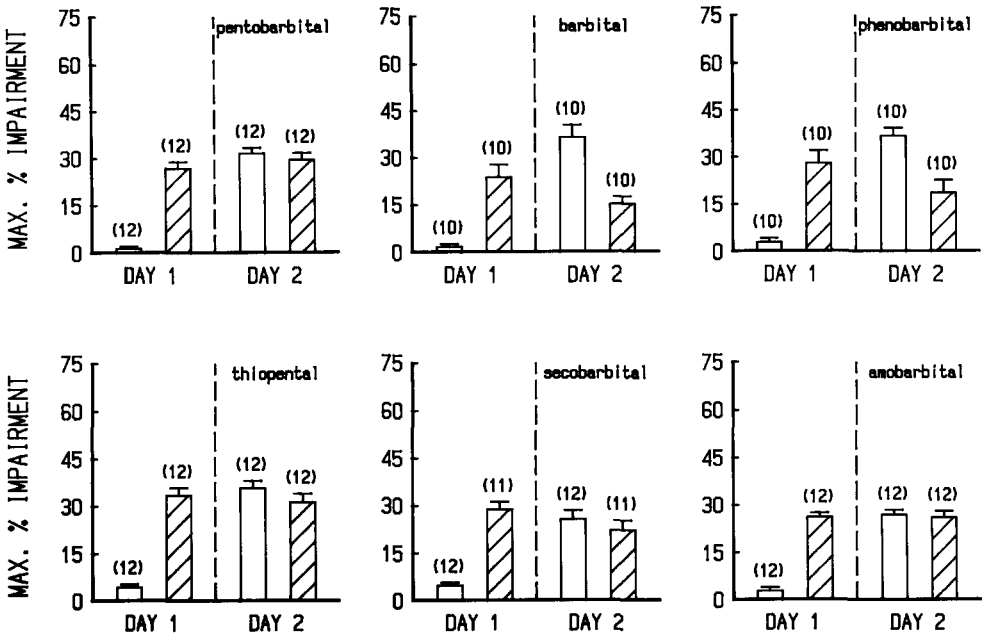

FIG. 4. Maximum percentage impairment (tilt-plane test) in rats given saline or ethanol on day 1 as described in Fig. 3. On day 2, both groups were injected IP with pentobarbital (23 mg/kg), barbital (120 mg/kg), phenobarbital (23 mg/kg), thiopental (25 mg/kg), secobarbital (16 mg/kg), or amobarbital (28 mg/kg). Drug labeling at top of the figures, symbols, and error bars are as described in Fig. 1.

animals returned to values not significantly different from the initial day 1 value, indicating that any rapid tolerance in the preceding test periods had dissipated. The results on cross-tolerance between ethanol and various barbiturates are dependent on the type of barbiturate employed. Ethanol pretreatment produced cross-tolerance to the barbiturates with relatively low lipid solubility (barbital and phenobarbital), but not to the more highly lipid-soluble barbiturates tested (pentobarbital, thiopental, secobarbital, and amobarbital). These findings on rapid cross-tolerance are in good agreement with recent findings on chronic cross-tolerance. Chronic ethanol treatment resulted in cross-tolerance to various benzodiazepines irrespective of their lipid solubility, whereas the development of cross-tolerance to barbiturates and to higher alcohols appeared to be related to their respective lipid:water partition coefficients (11); full details of that work will be published separately.

Similar findings were reported by Newman et al. (14) and Curran et al. (6), who showed cross-tolerance to diazepam, barbital, and phenobarbital in chronically alcohol-fed rats compared to their pair-fed controls, but negligible cross-tolerance to more highly lipid-soluble barbiturates such as thiamylol, methohexital, secobarbital, and thiopental. In other studies, Chan et al. (3) reported a similar degree of cross-tolerance to chlordiazepoxide in mice pretreated with ethanol 24 h earlier compared to mice chronically treated with ethanol on a liquid diet for 15 days. Although none of these studies specifically examined benzodiazepines differing in lipid solubility, chlordiazepoxide and diazepam do differ markedly in this respect (9) yet both showed cross-tolerance to ethanol.

Studies with genetically selected strains also seem to suggest that lipid solubility might be a critical factor in relation to alcohols and barbiturates, but not with respect to benzodiazepines. Harris and Allan (10) tested animals from three different pairs of selected lines: the long- and short-sleep (LS/SS) mice, the high- and low-acute ethanol sensitivity (HAS/LAS) rats, and the diazepam-sensitive and -resistant (DS/DR) mice, as well as heterogeneous stock (HS) mice. They found that ethanol insensitivity appears to be linked to reduced sensitivity to flunitrazepam and phenobarbital but not to pentobarbital. In other studies, Suzdak et al. (15) examined a series of short-chain alcohols for their ability to stimulate GABA receptor-mediated ^{36}Cl uptake and compared these values to previously reported data on their intoxication potencies in rats. All the alcohols tested stimulated chloride uptake (at concentrations that occur during acute intoxication), and their potencies in stimulating GABA receptor-mediated chloride uptake were highly correlated with both their intoxication potencies in rats and their membrane:buffer partition coefficients.

Drug levels for various alcohols, barbiturates, and benzodiazepines were not examined in the present study. It is therefore not possible to comment on the relative contribution of pharmacodynamic vs. pharmacokinetic factors to the rapid tolerance observed. However, previous investigations failed to show any pharmacokinetic basis for rapid tolerance to ethanol or for cross-tolerance between ethanol and pentobarbital (5,12). In our recent studies on cross-tolerance to various alcohols, barbiturates, and benzodiazepines in a chronic model of alcohol tolerance, we reported that pharmacokinetic alterations did not contribute significantly to the observed cross-tolerance (11). In another recent study, Chan et al. (4) concluded that metabolic tolerance is unlikely to play an important role in chronic cross-tolerance from ethanol to chlordiazepoxide. Therefore, it seems even less likely that a single administration of ethanol, given 24 h earlier, would result in altered disposition of these drugs.

These findings on rapid tolerance and rapid cross-tolerance suggest that rapid tolerance might prove to be a useful, inex-

pensive, and rapid tool to examine chronic tolerance. If this should prove to be true, it would offer many advantages. Studies involving chronic treatment of animals are considerably more costly than those involving only two doses and tests. Chronic treatment may also lead to ill effects due to repeated alcohol or drug administration. In experiments in which the influence of a pharmacological manipulation is being studied, the repeated administration of the manipulating agent may result in toxicity or tolerance, thus confounding the final outcome. The probability of such interaction between treatment regimen and the manipulating agent is less likely in the rapid tolerance model, which may therefore permit a better evaluation of the effect of the manipulating agent on tolerance development.

Unfortunately, no conclusion can yet be drawn. Chronic tolerance and cross-tolerance can be produced by various paradigms, which introduce such factors as intoxicated practice, conditional linkage with drug-predictive environmental cues, and high-dose drug treatment without these behavioral influences. Rapid tolerance is also subject to the influence of learning in the form of intoxicated practice (2) or previous test experience (7). It is not yet known whether the tolerance produced by these various paradigms rests on the same or on different neural adaptive mechanisms. Whether the predictive value of rapid tolerance will apply equally to all forms of chronic tolerance and cross-tolerance cannot be ascertained until experimental comparisons have been carried out with all models.

REFERENCES

1. Arvola, A.; Sammalisto, L.; Wallgren, H. A test for level of alcohol intoxication in the rat. Q. J. Stud. Alcohol 19:563–572; 1958.
2. Bitrán, M.; Kalant, H. Learning factor in rapid tolerance to ethanol-induced motor impairment. Pharmacol. Biochem. Behav. 39:917–922; 1991.
3. Chan, A. W. K.; Schanley, D. L.; Aleo, M. D.; Leong, F. W. Cross-tolerance between ethanol and chlordiazepoxide. Alcohol 2:209–213; 1985.
4. Chan, A. W. K.; Schanley, D. L.; Langan, M. C.; Leong, F. W.; Penetrante, M. L. Chronic treatment with ethanol and chlordiazepoxide alters the metabolism of chlordiazepoxide. Pharmacol. Biochem. Behav. 35:363–366; 1990.
5. Crabbe, J. C.; Rigter, H.; Uijlen, J.; Strijbos, C. Rapid development of tolerance to the hypothermic effect of ethanol in mice. J. Pharmacol. Exp. Ther. 208:128–133; 1979.
6. Curran, M. A.; Newman, L. M.; Becker, G. L. Barbiturate anesthesia and alcohol tolerance in a rat model. Anesth. Analg. 67: 868–871; 1988.
7. File, S. E.; Mabbutt, P. S.; Hitchcott, P. K. Characterisation of the phenomenon of "one-trial tolerance" to the anxiolytic effect of chlordiazepoxide in the elevated plus-maze. Psychopharmacology (Berl.) 102:98–101; 1990.
8. Gougos, A.; Khanna, J. M.; Lê, A. D.; Kalant, H. Tolerance to ethanol and cross-tolerance to pentobarbital and barbital. Pharmacol. Biochem. Behav. 24:801–807; 1986.
9. Greenblatt, D. J.; Shader, R. I.; Abernethy, D. R. Current status of benzodiazepines. N. Engl. J. Med. 309:354–358; 1983.
10. Harris, R. A.; Allan, A. M. Neurochemistry of alcohol sensitivity: Genetics and brain chloride channels. In: Kiianmaa, K.; Tabakoff, B.; Saito, T., eds. Genetic aspects of alcoholism (Proceedings of the Satellite Symposium "Alcohol and Genetics," Sapporo, Japan, June 23–24, 1988, Fourth Congress of the International Society for Biomedical Research on Alcoholism, vol. 37. Helsinki, Finland: The Finnish Foundation for Alcohol Studies; 1989:219–228.
11. Khanna, J. M.; Kalant, H.; Shah, G. Tolerance to ethanol and cross-tolerance to other alcohols, barbiturates and benzodiazepines. Toronto: International Society for Biomedical Research on Alcoholism, Abstract 317; 1990.
12. Khanna, J. M.; Kalant, H.; Shah, G.; Weiner, J. Rapid tolerance as an index of chronic tolerance. Pharmacol. Biochem. Behav. 38:427–432; 1991.
13. Khanna, J. M.; Lê, A. D.; Gougos, A.; Kalant, H. Effect of chronic pentobarbital treatment on the development of cross-tolerance to ethanol and barbital. Pharmacol. Biochem. Behav. 31:179–186; 1988.
14. Newman, L. M.; Curran, M. A.; Becker, G. L. Effects of chronic alcohol intake on anesthetic responses to diazepam and thiopental in rats. Anesthesiology 65:196–200; 1986.
15. Suzdak, P. D.; Schwartz, R. D.; Skolnick, P.; Paul, S. M. Alcohols stimulate GABA receptor-mediated chloride uptake in brain vesicles: Correlation with intoxication potency. Brain Res. 444: 340–345; 1987.