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Tolerance to the Anticonvulsant Effects of Phenobarbital, Trimethadione, and Clonazepam in Kindled Rats: Cross Tolerance to Carbamazepine[1]

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KIM, C. K., J. P. J. PINEL, M. M. HUDDA, D. J. WONG AND A. YUNG. *Tolerance to the anticonvulsant effects of phenobarbital, trimethadione, and clonazepam in kindled rats: Cross tolerance to carbamazepine.* PHARMACOL BIOCHEM BEHAV **41**(1) 115–120, 1992.—The kindled-convulsion model was used to assess the development of tolerance and cross tolerance to the anticonvulsant effects of antiepileptic drugs. In Experiment 1, tolerance developed to the anticonvulsant effects of bidaily (one every 48 h) IP injections of phenobarbital, trimethadione, and clonazepam on convulsions elicited 1 h after each injection in kindled rats by amygdala stimulation. In Experiment 2, kindled rats that were tolerant to the anticonvulsant effects of phenobarbital, trimethadione, or clonazepam received bidaily IP injections of carbamazepine, each followed 1 h later by a convulsive amygdala stimulation. There was a statistically significant transfer of tolerance from phenobarbital to carbamazepine, but not from either trimethadione or clonazepam to carbamazepine. Apparently, tolerance to anticonvulsant drugs is most likely to transfer between drugs that are effective against similar kinds of clinical and experimental seizures and have similar putative mechanisms of action.

Phenobarbital Trimethadione Clonazepam Carbamazepine Tolerance Cross tolerance Kindling Convulsion Seizure Anticonvulsant Rat Amygdala

KINDLED convulsions (13) have become a useful model for assessing the efficacy of anticonvulsant drugs [e.g., (1, 2, 22)] and the development of tolerance to them [e.g., (17,25)]. Kindled convulsions are particularly well suited to the study of tolerance to anticonvulsant drug effects because they produce little subject attrition and they vary little in form or duration either from subject to subject or from one convulsion to the next in the same subject [see (19)]. These characteristics of kindled convulsions are also advantageous in the study of cross tolerance to anticonvulsant drug effects [e.g., (26,41)], the phenomenon that was the focus of the present experiments.

The study of cross tolerance to anticonvulsant drugs can make two important contributions: one theoretical and one clinical. First, evidence of transfer of tolerance between drugs can provide strong evidence of a common mode of drug action; and second, knowledge of the patterns of cross tolerance between various anticonvulsant drugs may provide a basis for their effective prescription; most human epileptics are exposed to a variety of anticonvulsant drugs during the course of treatment [see (6)].

In the present experiments, we assessed the transfer of tolerance from phenobarbital, trimethadione, and clonazepam to carbamazepine. From among the many antiepileptic drugs in clinical use, these four drugs were selected for study on the basis of three criteria. (a) The first was their efficacy against the different types of clinical seizures [see (6, 30, 33)]: Carbamazepine is the drug of choice for the treatment of partial seizures and generalized tonic-clonic seizures; phenobarbital is also used against these same seizure types, but its profile of effectiveness is somewhat broader; trimethadione was the drug of choice for the treatment of absence seizures until the introduction of the less toxic succinimides; and clonazepam is used in the treatment of most seizure disorders although it is most effective against absence seizures. (b) The second criterion was their profile of effectiveness against maximal electroshock-induced and subcutaneous pentylenetetrazol-induced convulsions [see (30,33)]: Carbamazepine is more effective against electroshock convulsions than against convulsions induced by pentylenetetrazol; phenobarbital tends to be about equally effective against both; whereas trimethadione and clonazepam are more effective against pentylenetetrazol convulsions. (c) The third criterion was their different putative mechanisms of action; the following are some of the hypothesized mechanisms [see (3, 14, 18, 31, 39)]: Carbamazepine may act by decreasing sodium conductance and to a lesser extent calcium and potassium conductance; phenobarbital may act by decreasing sodium, calcium, and potassium conductance, enhancing GABA inhibition, and antagonizing glutamate excitation; clonazepam may act by enhancing GABA inhibition; and trimethadione's mechanism is unknown.

On the basis of the similarities and differences among the four drugs in the types of clinical seizures that they control, their

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relative effectiveness in suppressing maximal electroshock-induced convulsions and convulsions induced by subcutaneous pentylenetetrazol, and their putative mechanisms of action, we hypothesized that cross tolerance would be greatest between phenobarbital and carbamazepine, less between clonazepam and carbamazepine, and least between trimethadione and carbamazepine. The primary purpose of the present experiments was to test this hypothesis.

EXPERIMENT 1

The purpose of Experiment 1 was to demonstrate that tolerance develops to the anticonvulsant effects of phenobarbital, trimethadione, and clonazepam on convulsions elicited in kindled rats by amygdala stimulation, and in doing so to prepare the rats for the cross tolerance test to carbamazepine in Experiment 2. Evidence of tolerance to the anticonvulsant effects of each of these three drugs had been previously reported [e.g., (10, 12, 38); see (7,8) for reviews], but Experiment 1 constituted the first demonstration of tolerance to the anticonvulsant effects of phenobarbital and trimethadione on kindled convulsions.

METHOD

Subjects

The subjects in Experiment 1 were 57 adult male, 350 to 450 g, hooded Long-Evans rats obtained from Charles River, Canada. Each rat was individually housed in a standard stainless steel hanging cage with continuous access to Purina rat chow and water. All experimental manipulations occurred during the light phase of the 12:12-h light:dark cycle (lights on at 8:00 a.m.) at approximately the same time each experimental day.

Drugs

The drugs used in Experiment 1 were phenobarbital (30 mg/kg; in a sodium salt form; BDH Chemicals), trimethadione (270 mg/kg; Abbott Pharmaceuticals), and clonazepam (0.40 or 0.35 mg/kg; Hoffmann-La Roche). The doses employed were determined from previous published studies [e.g., (2,22)] and our own pilot observations. We attempted to select doses that were the minimum doses required to initially block the forelimb clonus elicited by amygdala stimulation in kindled rats. The vehicle was isotonic saline with 2% Tween 80 (J. T. Baker Chemical). All drug and vehicle injections were delivered intraperitoneally in a volume of 5 ml/kg. Sonification was employed to get trimethadione into suspension and clonazepam into solution.

Surgery

Following the administration of sodium pentobarbital (65 mg/kg, IP) anesthesia, a single chronic bipolar electrode (Plastic Products Company, MS-303-2) was stereotaxically directed at the left basolateral amygdala of each rat [2.8 mm posterior, 5.0 mm to the left, and 8.7 mm ventral to the skull surface at bregma, with the incisor bar set at −3.3 mm; coordinates from (24)]. It was secured to the skull with stainless steel screws and dental acrylic. Tetracycline was sprinkled over the incision before suturing.

Kindling Phase

After at least 5 days of postsurgical recovery, each of the 57 rats was stimulated (400 μA, 60 Hz, 1 s) three times per day, 5 days a week for 3 weeks, with at least 2 h separating consecutive stimulations. At first the stimulations produced no behavioral response other than a momentary cessation of ongoing activity, but by the end of this regimen of 45-kindling stimulations, each stimulation produced a stereotypical generalized clonic convulsion [see (29,32)]. Several different features of each kindled convulsion were recorded, but the measure of convulsion intensity on which the analysis focused was the duration of forelimb clonus. This measure is positively correlated with other measures of kindled convulsion severity (e.g., convulsion class); it is particularly reliable; and it responds systematically to a variety of pharmacological manipulations [e.g., (20, 27, 28)]. Electrographic activity was not monitored. During the kindling phase, three subjects were eliminated from the experiment: one became ill and two rejected their electrode assemblies. The remaining rats progressed to the no-drug baseline phase.

No-Drug Baseline Phase

The no-drug baseline phase began 48 h following the last of the 45-kindling stimulations; it comprised four stimulations, one every 48 h (±2 h). This bidaily stimulation schedule, once initiated during the baseline phase, was maintained for the duration of the experiment. Each rat was injected with the saline vehicle 1 h prior to the fourth and last no-drug baseline stimulation; this fourth no-drug baseline trial served as the no-drug baseline test. Two rats that did not display more than 20 s of forelimb clonus on the no-drug baseline test were not studied further.

Drug Baseline Test

The remaining rats were divided randomly into three groups, and then 48 h after the no-drug baseline test, each rat received either phenobarbital (n = 18), trimethadione (n = 17), or clonazepam (0.40 mg/kg; n = 17) 1 h prior to the scheduled amygdala stimulation. Rats that displayed more than 20 s of forelimb clonus on the drug baseline test were not studied further: one rat in each of the phenobarbital and trimethadione conditions, and two rats in the clonazepam condition did not meet this criterion.

Tolerance-Development Phase

In the 48-h interval between the drug baseline test and the beginning of the tolerance-development phase, the rats in each of the three drug conditions were divided into a drug group and a corresponding vehicle control group. The subjects were assigned to groups in such a way that each of the drug groups and its corresponding vehicle control group had the same mean body weight and approximately the same mean duration of forelimb clonus on both the no-drug baseline test and the drug baseline test.

On each of the bidaily tolerance-development trials, the same drug that had been injected on the drug baseline test was delivered to the rats in each of the three drug groups 1 h before a convulsive stimulation. The rats in each of the three vehicle control groups were treated similarly, but they received vehicle injections. There were 10 tolerance-development trials for the phenobarbital and trimethadione rats and 21 for the clonazepam rats. For clonazepam, the dose administered on the drug baseline test and on the first 15 tolerance-development trials was 0.40 mg/kg, but this was lowered to 0.35 mg/kg for the last six trials because the data suggested that the 0.40 mg/kg dose was too high to permit the observation of tolerance. The bidaily schedule was employed to reduce the possibility of drug accumulation [see (16,23)].

Drug Tolerance Test

The drug tolerance test occurred 48 h after the last tolerance-development trial. Each rat received the same drug that it had

received on the drug baseline test 1 h before a convulsive stimulation, so that the degree of tolerance to the anticonvulsant effect of the drug could be assessed in each of the three drug groups and in their respective vehicle control groups. The test dose of clonazepam was 0.35 mg/kg.

Statistical Analysis

Because the data were not parametric, the statistical significance of the results was assessed with Wilcoxon-Mann-Whitney tests (40) for between-group comparisons and Sign tests (40) for within-subject comparisons ($p<0.05$, one tailed). Only those subjects that completed the experiment were included in the statistical analysis: 9 rats in the phenobarbital group and 8 in its vehicle control group, 8 rats in the trimethadione group and 8 in its vehicle control group, and 8 rats in the clonazepam group and 7 in its vehicle control group.

RESULTS

As illustrated in the three panels of Fig. 1, tolerance developed to the anticonvulsant effects of phenobarbital (Panel A), trimethadione (Panel B), and clonazepam (Panel C). Before the tolerance-development phase, none of the three drug groups differed from its corresponding vehicle control group in either its responsiveness to the convulsive stimulation on the no-drug baseline test or to its responsiveness to the anticonvulsant effect of the drug on the drug baseline test (the subjects were originally subdivided into drug and vehicle control groups on the basis of these two measures). However, on the tolerance test, following the tolerance-development phase, the rats in each of the drug groups displayed substantial tolerance, whereas the rats in the respective vehicle control groups did not.

In the phenobarbital and trimethadione conditions, the statistical significance of the tolerance was established by both within-subject and between-group comparisons; however, in the clonazepam condition, it rested solely on a between-group comparison because the adjustment of the dose of clonazepam during the tolerance-development phase rendered before-and-after within-subject statistical comparisons uninterpretable. Three Wilcoxon-Mann-Whitney tests established that the rats in the phenobarbital ($p<0.004$), trimethadione ($p<0.0003$), and clonazepam ($p<0.027$) groups displayed significantly longer forelimb clonus on the tolerance test than did the rats in their respective vehicle control groups. Moreover, the rats in the phenobarbital (Sign test; $p<0.001$) and trimethadione (Sign test; $p<0.004$) groups displayed significantly longer forelimb clonus durations on the drug tolerance test than they had on the drug baseline test. There was no statistically significant decrease in the magnitude of the anticonvulsant drug effect between the drug baseline test and the drug tolerance test in the phenobarbital or trimethadione vehicle control groups (Sign test; $p>0.05$); this comparison could not be made in the clonazepam vehicle control group because of the change of dose.

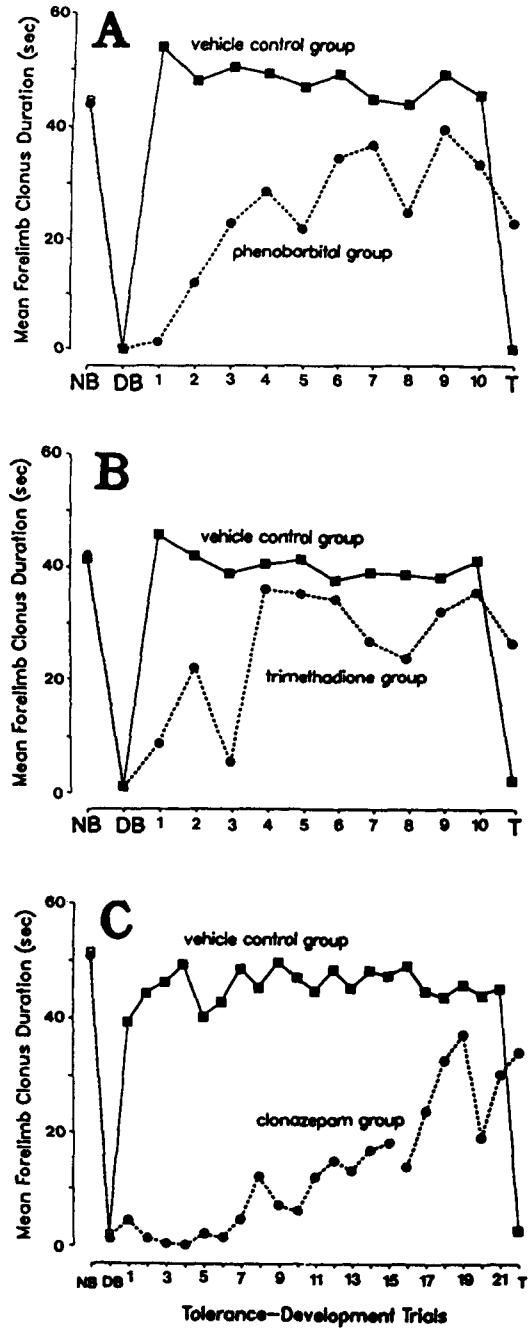

FIG. 1. Tolerance to the anticonvulsant effects of phenobarbital (Panel A), trimethadione (Panel B), and clonazepam (Panel C) on amygdala-kindled convulsions in rats. On the no-drug baseline test (NB), each stimulation elicited about 45 s of forelimb clonus; on the drug baseline test (DB), each drug exerted a potent anticonvulsant effect on every rat; and on the drug tolerance test (T), the three drug groups, but not the three corresponding vehicle control groups, displayed tolerance to the anticonvulsant drug effects.

DISCUSSION

The results of Experiment 1 confirm previous reports of tolerance to the anticonvulsant effects of phenobarbital [e.g., (9,38)], trimethadione (5,10), and clonazepam [e.g., (12,36)]. Experiment 1 constitutes the first demonstration of tolerance to the anticonvulsant effects of phenobarbital and trimethadione on kindled convulsions, but three previous studies had demonstrated tolerance to the anticonvulsant effect of clonazepam on kindled convulsions (35, 43, 44).

Tolerance seemed to have developed more slowly to clonazepam than it did to phenobarbital and trimethadione, but caution must be exercised in interpreting this difference. Although we attempted to select equipotent doses of the three drugs (i.e., the minimum effect doses) on the basis of previous reports and

a few unsystematic pilot observations, there is no guarantee that we accomplished this goal. Accordingly, differences in the rate of tolerance development could reflect the specific doses that were employed rather than general properties of the drugs.

Experiment 1 did not assess whether the observed tolerance was due to functional changes, dispositional changes, or some combination of the two. However, in previous experiments, tolerance to the anticonvulsant effects of trimethadione (10) and clonazepam [e.g., (35,37)] has been shown to be due to functional changes alone. Tolerance to the anticonvulsant effect of phenobarbital has been attributed mainly to functional changes [e.g., (38)], although it has been suggesed that dispositional changes may play a minor role (9).

EXPERIMENT 2

Despite the fact that most epileptic patients are exposed to a variety of anticonvulsant drugs during the course of their treatment (i.e., to polypharmacy), cross tolerance between anticonvulsant drugs has only rarely been studied. The purpose of Experiment 2 was to assess the transfer of tolerance from phenobarbital, clonazepam, and trimethadione to carbamazepine. The transfer of tolerance from the anticonvulsant effect of phenobarbital to carbamazepine has been demonstrated (21), but Experiment 2 was the first to assess the transfer of tolerance to anticonvulsant effects from trimethadione and clonazepam to carbamazepine. We hypothesized on the basis of their relative effectiveness against clinical seizures, their relative effectiveness against maximal electroshock-induced and subcutaneous pentylenetetrazol-induced convulsions, and their putative mechanisms of action that cross tolerance to anticonvulsant effects would be greatest from phenobarbital to carbamazepine, less from clonazepam to carbamazepine, and least from trimethadione to carbamazepine.

METHOD

Subjects

The subjects in Experiment 2 were the rats that had completed Experiment 1. The three drug groups in Experiment 1 remained intact: phenobarbital (n = 9), trimethadione (n = 8), and clonazepam (n = 8). The three vehicle control groups from Experiment 1 were combined into one group (n = 23); a rat's particular control condition in Experiment 1 had no effect on its performance in Experiment 2.

Procedure

The assessment of cross tolerance began 48 h after the completion of Experiment 1. The rats in all four groups (the three drug groups and the vehicle control group) received 10 bidaily IP injections of carbamazepine (35 mg/kg; Geigy Pharmaceuticals), each followed 1 h later by a convulsive stimulation. Note that the dose of carbamazepine was half that employed previously (19); a dose-response pilot study suggested that 35 mg/kg of carbamazepine was nearer the minimal dose that is required to block forelimb clonus in amygdala-kindled rats. The carbamazepine was sonified and injected as a suspension in a 2% Tween 80 and isotonic saline vehicle; all injections were delivered in the same volume (5 ml/kg). Cross tolerance to carbamazepine was assessed in two ways: by the inability of the first injection of carbamazepine to suppress forelimb clonus and by the rate at which each subject achieved an a priori criterion of tolerance to carbamazepine. The criterion of tolerance was forelimb clonus on two consecutive trials that was at least 50% as long as that displayed by the same rat on the no-drug baseline test of Experiment 1.

Histology

At the conclusion of Experiment 2, all surviving subjects were killed with CO_2. Their brains were removed, preserved in formalin, frozen, sliced along the coronal plane, mounted on slides, and then stained with cresyl violet. Each of the electrodes was found to terminate in the left amygdala or near its boundary.

Statistical Analysis

Kruskal-Wallis one-way analysis of variance (40) was used to establish the overall significance of the differences among the four groups ($p<0.05$). This was followed by nonparametric multiple comparisons between individual groups if statistical significance ($p<0.05$, two-tailed) was achieved. The significance of within-subject changes was assessed by a series of Sign tests [(40); $p<0.05$, one-tailed].

RESULTS

The results of Experiment 2 are summarized in Fig. 2. The mean duration of the forelimb clonus elicited in each group by the convulsive stimulation after the first and the last (10th) carbamazepine injections is illustrated in Panel A, and the mean number of trials taken by each group to achieve the criterion of tolerance is illustrated in Panel B. Inspection of either panel of Fig. 2 indicates that our experimental hypothesis was confirmed: subjects tolerant to the anticonvulsant effect of phenobarbital were totally cross tolerant to the anticonvulsant effect of carbamazepine, those tolerant to trimethadione displayed no cross tolerance whatsoever, and those tolerant to clonazepam displayed an intermediate level of cross tolerance.

Statistical analyses confirmed the story told by Fig. 2. The results of Kruskal-Wallis tests indicated that there were significant overall differences among the groups in the duration of forelimb clonus on the first carbamazepine trial ($p<0.001$) and in the mean number of carbamazepine injections required to achieve the a priori criterion of cross tolerance ($p<0.001$). Subsequent multiple comparisons revealed that the rats of the phenobarbital group displayed significantly more cross tolerance to carbamazepine than the rats of the vehicle control group ($p<0.05$ on both measures), whereas the rats in the trimethadione ($p>0.05$ on both measures) and clonazepam ($p>0.05$ on both measures) groups did not. Interestingly, the rats in the trimethadione group actually displayed less forelimb clonus on the first trial and took longer to reach the criterion of tolerance than did the rats in the vehicle control group, although neither of these differences was statistically significant. The phenobarbital group was significantly more tolerant to carbamazepine than was the trimethadione group ($p<0.05$ on both measures). Two rats in the trimethadione group and one in the vehicle control group did not reach the criterion of cross tolerance over the 10 trials and were assigned a score of 10 for the purpose of calculating the means. There were no significant differences among the four groups on the final (10th) cross-tolerance trial (Kruskal-Wallis; $p>0.05$).

Sign tests indicated that the within-subject decrease observed between the first to the last (10th) injection in carbamazepine's ability to block forelimb clonus was significant for the trimethadione ($p<0.008$) and saline ($p<0.002$) groups, but not for the phenobarbital ($p>0.05$) and the clonazepam ($p<0.05$) groups.

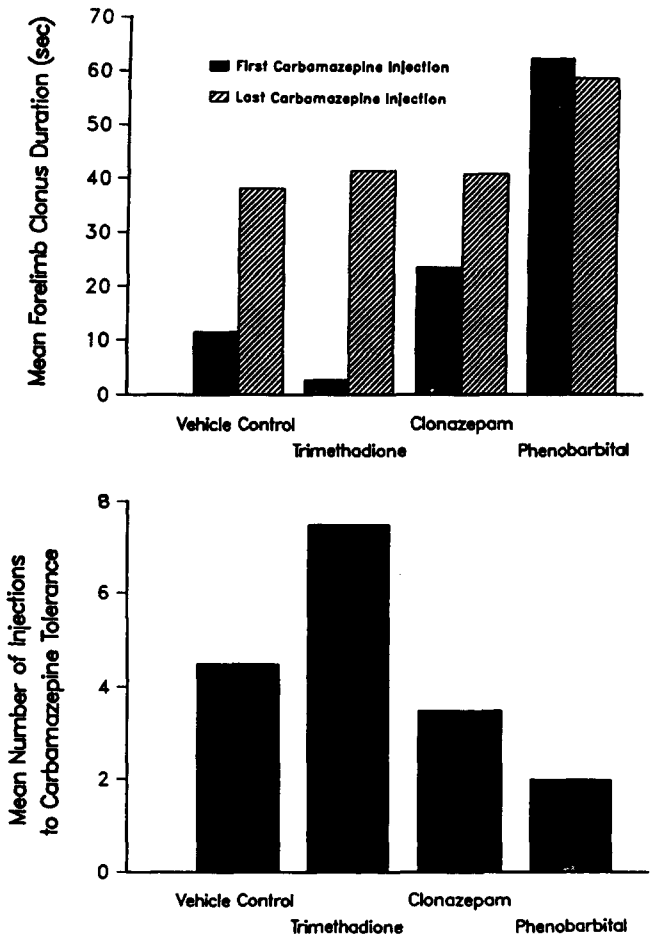

FIG. 2. The statistically significant transfer of tolerance to the anticonvulsant effect of carbamazepine from pentobarbital, but not from either trimethadione or clonazepam. Panel A illustrates the ability of the first and last (10th) injection of carbamazepine to block the forelimb clonus elicited by stimulation of the amygdala in each of the three drug groups. Panel B illustrates the mean number of injections that it took for each drug group to achieve an a priori criterion of carbamazepine tolerance.

DISCUSSION

In Experiment 1, tolerance developed to the anticonvulsant effects of phenobarbital, trimethadione, and clonazepam on kindled convulsions. In Experiment 2, there was statistically significant transfer of this tolerance from phenobarbital to carbamazepine, but not from either trimethadione or clonazepam to carbamazepine. This pattern of transfer (see Fig. 2) was predicted on the basis of the assumption that tolerance to anticonvulsant drug effects would transfer best between drugs that have a similar profile of effectiveness against various kinds of clinical and experimental seizures and have similar putative mechanisms of action.

Studies of cross tolerance to anticonvulsant drug effects have been few. Masuda et al. (21) demonstrated significant transfer of tolerance from phenobarbital to carbamazepine and from phenobarbital to diphenylhydantoin on maximal electroshock-induced convulsions; but there was no significant transfer from phenobarbital to sulfamoylmethyl benzisoxazole. Gent, Bentley, Feely and Haigh (11) demonstrated cross tolerance among the anticonvulsant effects of four benzodiazepines (clobazam, clonazepam, diazepam, and lorazepam), the significant transfer of tolerance from the four benzodiazepines to sodium valproate, but no significant transfer from the benzodiazepines to phenobarbital. Rosenberg, Tietz and Chiu (34) demonstrated the transfer of tolerance to anticonvulsant drug effects from flurazepam to diazepam; Bourgeois (4), from primidone to its metabolite phenobarbital; Vajda et al. (41), from clobazam to clonazepam; and Pinel et al. (26), from pentobarbital to ethanol. Kim, Pinel and Roese (15) demonstrated that the cross tolerance between the anticonvulsant effects of bidaily (one every 48 h) pentobarbital and ethanol injections is both bidirectional and contingent on the administration of convulsive stimulation following each drug injection.

Because the purpose of Experiment 2 was to assess the transfer of tolerance to carbamazepine, it did not include a vehicle (no-carbamazepine) control group, and thus no firm conclusions can be reached about carbamazepine tolerance. Nevertheless, the statistically significant decrease that occurred over the 10 trials in the ability of carbamazepine to suppress the forelimb clonus of the rats in the saline-to-carbamazepine group, strongly suggests that tolerance develops to carbamazepine's anticonvulsant effect on kindled convulsions, thus confirming the recent report of Mana et al. (19).

GENERAL DISCUSSION

In Experiment 1, the kindled-convulsion model was used to demonstrate the development of tolerance to the anticonvulsant effects of three drugs: phenobarbital, clonazepam, and trimethadione. In Experiment 2, the kindling model was used to assess the transfer of tolerance from each of these three drugs to the anticonvulsant effect of carbamazepine. The transfer of tolerance from phenobarbital to carbamazepine was total; from clonazepam to carbamazepine, it was substantial but not statistically significant; and from trimethadione to carbamazepine, it was nonexistent. These results were predicted on the basis of the similarity between the drugs in their profile of effectiveness against various kinds of clinical seizures, in their relative effectiveness against maximal electroshock and subcutaneous pentylenetetrazol convulsions, and in their putative mechanisms of action. However, caution must be exercised in comparing the magnitude of these three cross-tolerance effects because only a single dose of each drug was studied.

It has been proposed that antiepileptic drugs fall into one of two general categories [see (30, 33, 42)]. If one assumes that tolerance transfers more readily between drugs of the same category, the present results confirm the categorization of phenobarbital and carbamazepine as type 1 antiepileptics, and clonazepam and trimethadione as type 2 antiepileptics. Type 1 antiepileptics are effective against partial seizures and generalized tonic-clonic seizures, they are effective against maximal electroshock convulsions, and they work by preventing the spread of seizure discharges from the focus. Type 2 antiepileptics are effective against generalized seizures (especially absence seizures), they are effective against subcutaneous pentylenetetrazol convulsions, and they work by increasing seizure threshold.

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