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BRIEF COMMUNICATION

Oxazepam Induced Mouse Killing by Rats

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LEAF, R. C., D. J. WNEK AND S. LAMON. *Oxazepam induced mouse killing by rats.* PHARMACOL BIOCHEM BEHAV 20(2) 311–313, 1984.—Oxazepam (2.5–80 mg/kg) induced significant mouse killing among large samples (N=100/dose) of Holtzman strain albino rats. Meprobamate (2.5–80 mg/kg) and Chlorpromazine (0.5–4 mg/kg) did not induce killing. Despite its lesser tendency to induce aggression in humans, Oxazepam is as potent as Chlordiazepoxide for inducing killing by rats. Induction of mouse killing by rats appears to the predict clinical potency rather than the aggressive side-effects of anxiolytic benzodiazepines.

Oxazepam Mouse killing Meprobamate Chlorpromazine Chlordiazepoxide

THE effects of clinically useful anxiolytic benzodiazepines on aggressive behaviors are puzzling. Although these compounds were first studied because of their "taming" effects in animals and their "tranquilizing" effects in humans [1,20] they can also induce aggressive behaviors. "Paradoxical" rage in humans, and its sometimes violent consequences, have been studied by a number of investigators (e.g., [2, 8, 12, 17, 22], and diverse forms of aggressive behavior in a variety of other species have also been identified (see [4] for a general review and [18,21]) for recent examples.

The incidence of aggressive effects of anxiolytic benzodiazepines in humans is not related to their therapeutic potency. Although these unwanted side-effects occur with noticeable frequency with some drugs of class, they do not occur with others. Oxazepam, in contrast to Chlordiazepoxide and Diazepam, produces little or no aggression in either experimental [6, 9, 13, 14] or clinical settings [2, 5, 10].

Whether the mechanisms of action of these drugs in nonhuman species parallels their actions in humans is not known, but it seems useful to determine whether the aggression-inducing effects of benzodiazepines in humans are related to, and could be predicted by, similar effects in other species. If Oxazepam proved to be less effective than Chlordiazepoxide in inducing a particular form of aggression in animals, this would suggest that the phenomenon was also a side-effect in the animal species. The animal behavior might be useful for pre-clinical prediction of side-effects likely to result during clinical studies with new compounds.

If, on the other hand, Oxazepam was as potent as Chlordiazepoxide in inducing some form of animal aggression which the latter is known to cause, this would suggest that the animal phenomenon was probably a reflection of the anxiolytic, or response-releasing, actions of the drugs [3]. The aggressive responses by animals, unlike those among humans, might, then reflect their clinically useful actions. In this case, while the results might be helpful for understanding the patterns of animal behavior, they would be less useful for pre-clinical testing because good methods for pre-clinical prediction of anxiolytic action are already available [15,23].

This report describes the effects of Oxazepam on mouse killing by rats, together with control data on Clordiazepoxide and some ancilliary studies with Meprobamate and Chlorpromazine. Our previous studies demonstrated that rats kill mice much more frequently after injections of Chlordiazepoxide or Diazepam than after placebo injections; such mouse killing, like "paradoxical" rage in humans, appears in only a small percentage of all subjects tested, no matter what doses are used [16]. Our basic finding here, described below, is that Oxazepam is as effective as Chlordiazepoxide for inducing these low, but significant, rates of killing. These results suggest that the common, clinically predictive, rather than differential, side-effect predictive, actions of various benzodiazepines cause induction of mouse killing by rats.

METHOD

Animals

The animals studied were 2200 adult male Holtzman strain albino rats (200–500 g).

Procedure

Three separate studies were carried out with techniques identical to those used by [16]. Each study included a placebo (vehicle alone) control group, a drug (previously known to be effective at the dose used) control group, and groups given various doses of the test drug to be investigated. One hundred rats were used for each control group and for each dose of each test drug. Each rat was given its appropriate injection, IP, and this was followed immediately by a test for mouse killing as described by [25]. During killing tests, a single Swiss-Webster mouse was placed in the rat's home cage until either (a) it was killed, or (b) a maximum of 2 hr without a kill occurred.

The first study included 8 groups. These were given 1 ml/kg or 0.9% NaCl plus 0.5% Tween 80 (placebo, vehicle, control group) or the vehicle plus 20 mg/kg plus 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg or Oxazepam HCl (test drug groups).

The second study also included 8 groups. These were given 1 ml/kg of 0.9% NaCl plus Tween 80 (placebo, vehicle, control group), or the vehicle plus 7.5 mg/kg Chlordiazepoxide (drug control group), or the vehicle plus 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg of Meprobamate (test drug groups).

The third study included 6 groups. These were given 1 ml/kg of 0.9% NaCl (placebo, vehicle, control group), or vehicle plus 30 mg/kg Pilocarpine HCl (drug control group), or vehicle plus 0.5 mg/kg, 2 mg/kg, or 4 mg/kg Chlorpromazine HCl (Chlorpromazine) (test drug groups).

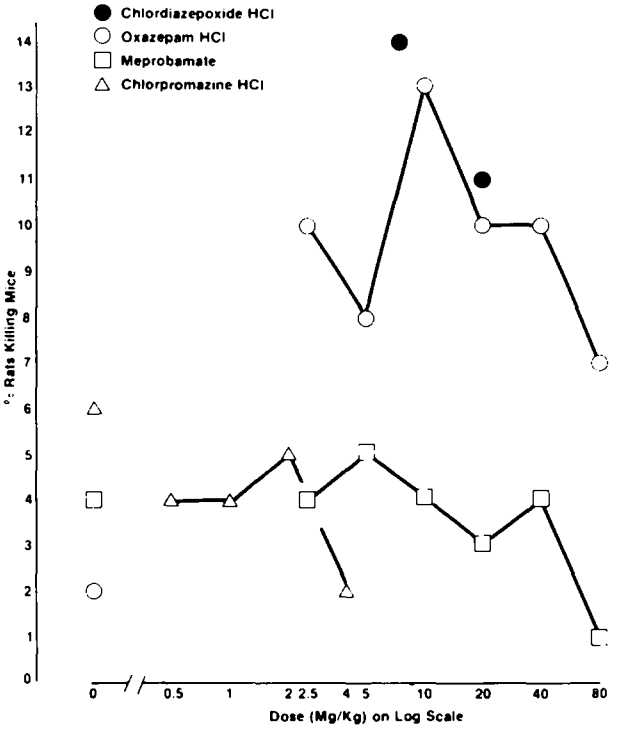

FIG. 1. Killing rates for tested drugs.

RESULTS

The results from all groups from all three studies, except for the drug control group given Pilocarpine, are shown in Fig. 1. The Pilocarpine drug control group had 48 rats that killed mice (48%), a value far outside the range of all other groups tested. Among the other conditions, only two drugs induced significant amounts of killing. Oxazepam, at every dose tested, and both the 7.5 and 20 mg/kg control doses of Chlordiazepoxide induced killing at rates higher than the upper bound of the 95% confidence interval for killing among their placebo controls. Meprobamate did not induce killing, and Chlorpromazine actually decreased the low spontaneous killing rates observed among the placebo controls.

The results from both placebo and drug control groups are not significantly different from those reported previously with the test conditions used here [7, 16, 24, 25].

DISCUSSION

The results of these experiments, together with those reported previously by [16], suggest that the induction of mouse killing by rats is related to the clinical, rather than side, effects of Benzodiazepines. Oxazepam, in this study, was approximately equal to Chlordiazepoxide in potency. This similarity in the effectiveness of the two Benzodiazepines parallels their clinical efficacy. It does not parallel the difference between the two drugs in inducing aggressive side effects in humans. The failure of Meprobamate and Chlorpromazine to induce killing, and of Pentobarbital, which we reported previously [16], indicates that the induction of killing is not due to depressant actions that the Benzodiazepines may share with other psychotropic drugs.

The dose-effect function for induction of killing by Oxazepam seems similar to that for Chlordiazepoxide and Diazepam [16]. All three Benzodiazepines induce significant killing at very low doses. Higher doses induce further increments in killing, but doses high enough to inhibit spontaneous killing [11,19] result in less total killing than the lower doses. At the higher doses, these drugs could be described as having a mixed, both facilitatory and inhibitory, effect on killing. The inhibitory component, which causes the descending limb of the inverted U-shaped dose-effect function, seems to be due to the non-specific motor side-effects of the drug. The facilitatory compoennt, which causes the ascending limb, seems to reflect the selective, response releasing, psychotropic actions.

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