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BRIEF COMMUNICATION

Effects of Methsuximide on Schedule-Controlled Responding in the Pigeon

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DELANEY, D , V PELLETTIERE, H SCHLINGER AND A POLING *Effects of methsuximide on schedule-controlled responding in the pigeon* PHARMACOL BIOCHEM BEHAV **29**(3) 641–644, 1988 —Acute and chronic effects of methsuximide (25, 50, 75, and 100 mg/kg), a succinimide with anticonvulsant properties, were examined in pigeons responding under a multiple fixed-ratio 50 fixed-interval 90-sec schedule of food delivery The clearest acute effect of methsuximide was a substantial reduction in response rates under both components of the multiple schedule when the drug was administered at 100 mg/kg Detailed analysis of the temporal distribution of responding under the fixed-interval failed to reveal rate-dependent drug effects Tolerance appeared to develop to the effects of methsuximide when the drug was administered chronically

Methsuximide Pigeons Multiple schedule Fixed-ratio schedule Fixed-interval schedule

DRUGS from several chemical classes, including succinimides, hydantoins, and barbiturates, are used in the clinical management of epilepsy Interestingly, drugs from the same chemical class may differ with respect to the kinds of seizures they control For example, one succinimide, methsuximide, is very effective in blocking maximal electroshock seizures, but another succinimide, ethosuximide, is minimally effective in blocking such seizures [1] Methsuximide also has a much wider spectrum of antiepileptic activity than ethosuximide [12]. This suggests that methsuximide has neuropharmacological actions in addition to or different from those of ethosuximide [4] If this is so, the two agents might well differ with respect to their behavioral effects.

No comparison of the behavioral effects of methsuximide and ethosuximide in humans has appeared Nonhuman data, however, suggest that the actions of the drugs differ in pigeons responding under a repeated acquisition procedure In this assay, ethosuximide had little or no effect on learning (percent errors), even at doses that substantially reduced response rates [7]. Methsuximide, in contrast, interfered with learning at doses that reduced response rates [2] In order to allow for further comparison of the behavioral effects of methsuximide and ethosuximide, the present investigation examined the effects of methsuximide in pigeons responding under a multiple fixed-ratio 50 fixed-interval 90-sec (mult FR 50 FI 90-sec) schedule of food delivery. The two components of this schedule characteristically engender different rates and temporal patterns of responding. Drug effects often differ as a function of rate and pattern of responding in the absence of drug and the mult FR FI schedule has proven useful in discerning rate-dependent drug effects as well as general drug-induced behavioral impairment [3, 5, 14] The effects of ethosuximide under this schedule have previously been reported [10], but those of methsuximide have not

METHOD

Subjects and Apparatus

Three experimentally-naive female White Carneaux pigeons, maintained at 80% of free-feeding weights, served as subjects Each was individually housed with unlimited access to grit and water

Subjects were tested in three computer-controlled operant conditioning chambers described in detail elsewhere [5] Each chamber contained a food hopper and three response keys, only the center key was lighted and operative in this study.

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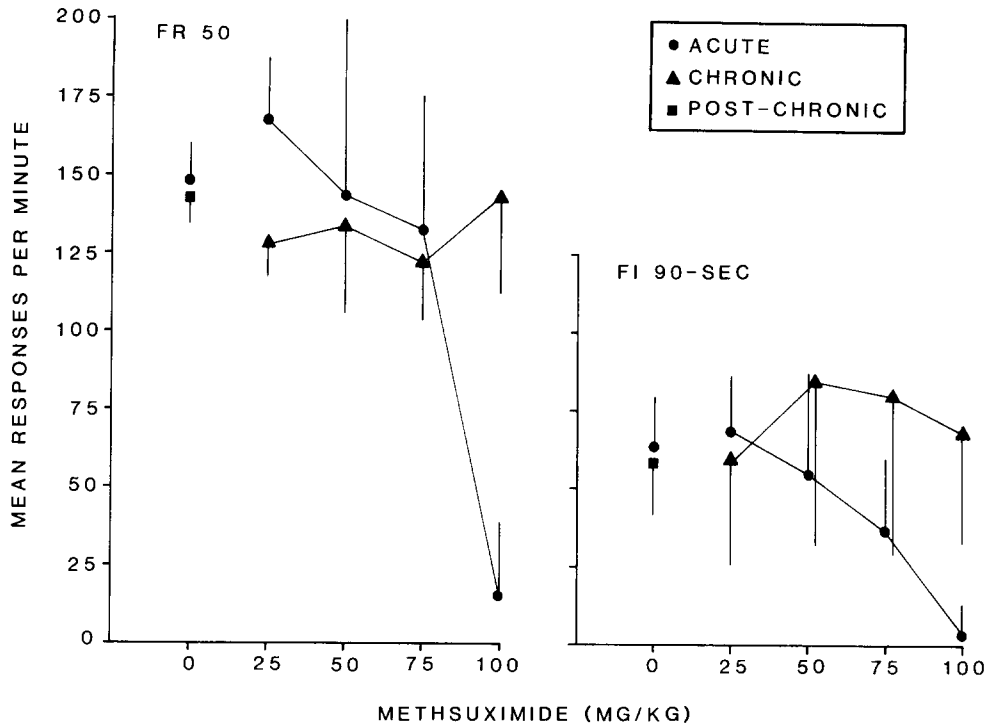

FIG 1 Mean group response rate (±1 standard error) under both components of a mult FR 50 FI 90-sec schedule of food delivery under all experimental conditions Acute control data (0 mg/kg) represent performance of 3 birds during 8 sessions (the control session prior to each of 4 doses, with each dose administered twice) Post-chronic control data (0 mg/kg) represent performance during the 5 sessions immediately following chronic exposure to methsuximide Acute drug data show average performance during 2 exposures to each dose Chronic drug data show average performance during a single exposure to each dose

Behavioral Procedure

Following initial keypeck training, subjects were exposed to a mult FR 50 FI 90-sec schedule of food delivery Under this schedule, the color of key illumination alternated at 5-min intervals, blue-green illumination accompanied the FI component and red illumination accompanied the FR component. Reinforcement (3-sec delivery of mixed grain) followed every 50th keypeck under the FR 50 component Under the FI 90-sec component, reinforcement followed the first response emitted at least 90 sec from the previous food delivery or the onset of blue-green key illumination Sessions were 30 min in duration and always began with the key illuminated in blue-green (i e , with the FI component in effect) A single session was conducted for each subject at about the same time each day 6 days per week

Pharmacological Procedure

Subjects were exposed to the mult FR 50 FI 90-sec schedule until the response rates of individual subjects under both components were stable The criterion for stability was three consecutive sessions in which response rates in each individual session were within 10% of the mean rate of responding across those three sessions When this criterion was met, acute dose-response determinations were begun Four doses of methsuximide (25, 50, 75, and 100 mg/kg), obtained from Warner-Lambert (Ann Arbor, MI) and dissolved in 80% propylene glycol and 20% ethanol, were evaluated In all phases of the study, drug (and control) injections were administered intramuscularly (IM) 30 min prior to experimental sessions, at an injection volume of 1 ml/kg Drug doses and the presession injection interval were selected on the basis of those used in a previous investigation of methsuximide [2] During acute dose-response determinations, each bird received all doses on two occasions Doses were given in an irregular order that varied across subjects All drug administrations were separated by at least three sessions in which responding was stable as defined above, one of these sessions was preceded by a control (saline) injection

Following completion of the acute dose-response determination, all birds received control injections prior to five consecutive sessions. Immediately thereafter, each bird received 50 (subjects S1 and S3) or 75 mg/kg (S2) methsuximide prior to each of 20 consecutive sessions The dose administered chronically to an individual subject was the lowest one that decreased response rate under either component of the mult schedule when given acutely Following the twentieth day of chronic exposure, the acute dose-response curve was replicated During this phase of the study, each dose was administered to all birds on a single occasion and all determinations were separated by three consecutive days in which the chronic dose was administered Five vehicle control sessions were arranged at the end of the study These were used to calculate a post-chronic baseline

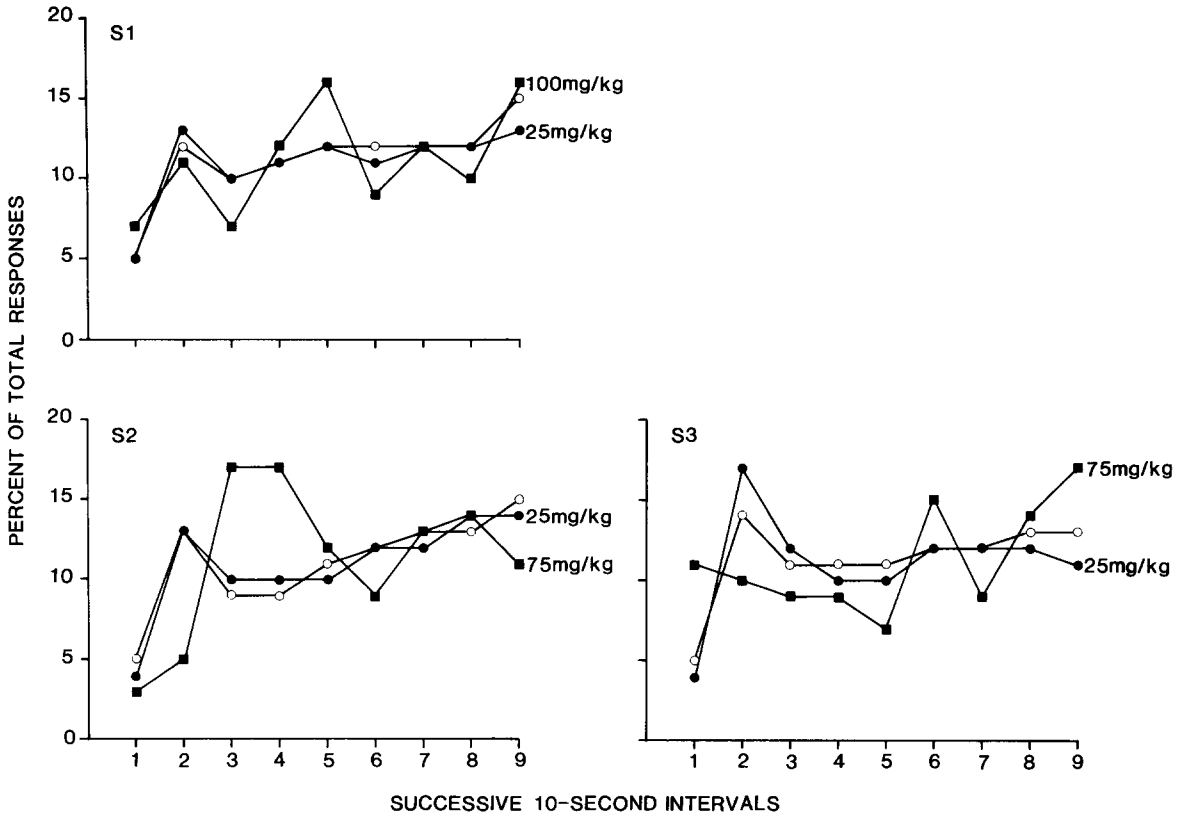

FIG 2 Effects of selected doses of methsuximide on the percent of total responses emitted by individual pigeons during successive 10-sec intervals of the FI 90-sec component Open circles indicate mean performance during the 8 control sessions that preceded acute drug administrations Closed circles show performance when the lowest dose of methsuximide (25 mg/kg) was administered acutely Squares indicate the temporal distribution of responding when a relatively high dose of methsuximide was administered For each bird, this high dose was that at which responding under the FI occurred at the lowest nonzero rate

RESULTS

During each session, response rates in the FR and FI components were recorded. In addition, the number of responses emitted in each of nine consecutive 10-sec segments of the FI 90-sec was recorded, this measure was taken to allow for an assessment of possible rate-dependent drug effects.

Figure 1 shows mean group response rates during all drug conditions and during acute and post-chronic baseline (control) conditions. Although baseline response rates were considerably higher under the FR component, drug effects were similar under the FR and FI components Statistical analysis (repeated measures analysis of variance) revealed significant drug effects under both the FR ($F=21\ 9, p<0.01$) and the FI ($F=10.8, p<0.01$) components The clearest acute effect of methsuximide was a substantial reduction in response rates when the drug was administered at 100 mg/kg. Planned-comparison tests (T_{LSD}) revealed that the mean group response rate at 100 mg/kg differed significantly from the control value under both the FR ($T=8\ 3, p<0.01$) and the FI ($T=4.8, p<0.01$) Mean group response rate at 75 mg/kg was also significantly less than the control value under the FI component ($T=2\ 2, p<0.05$), but not under the FR. Neither the 50 mg/kg dose nor the 25 mg/kg dose significantly affected responding under either component

The dose-response curve following chronic exposure to methsuximide was quite flat During the post-chronic dose-response determination, at all doses response rates under both components were within 1 SE of baseline (control) values

Figure 2 shows the effects of selected acute doses of methsuximide on the temporal distribution of responding under the FI component In the absence of drug, each bird responded at a higher rate as the FI progressed This characteristic pattern was not altered by acute administration of methsuximide

DISCUSSION

Although anticonvulsant drugs are widely and effectively used in the treatment of epilepsy, their behavioral side effects are understood poorly Clinical investigations have not revealed the precise behavioral actions of such medications, but they have demonstrated that anticonvulsants can produce deleterious changes in behavior. Recent investigations with nonhumans, reviewed elsewhere [6,8], indicate that there are qualitative as well as quantitative differences in the behavioral effects of various anticonvulsant drugs. These differences may be evident even when the agents in question are structurally similar This is apparent if one compares the effects of two succinimides, ethosuximide and

methsuximide, in pigeons responding under a repeated acquisition procedure Even at doses that substantially decreased response rates, the former agent had little effect on learning [7,9] The latter agent, in contrast, generally impaired learning at doses that reduced response rates [2]

Methsuximide and ethosuximide do not have equivalent actions under a repeated acquisition procedure Despite this, the present findings concerning the acute effects of methsuximide on response rates under a mult FR 50 FI 90-sec schedule of food delivery are similar to those previously reported for ethosuximide [10], although the latter agent appears to be slightly more potent Under this schedule, both drugs reduced responding at relatively high doses Neither drug produced clearly rate-dependent effects Although the 25 mg/kg dose of methsuximide was associated with an increase in responding under the FR component, but not the FI, which appears to suggest a rate-dependent action, the increase was not statistically significant Moreover, the drug failed to alter the temporal distribution of responding under the FI component The analysis of patterns of responding under FI schedules is a very popular method for studying rate-dependent drug actions, and drugs that produce such actions alter response distributions [14] Neither methsuximide nor ethosuximide did so, thus their actions do not appear to be rate-dependent

Chronic effects of ethosuximide under a mult FR FI schedule have not been reported, but tolerance reportedly developed to the drug's rate-decreasing effects in pigeons tested under repeated acquisition [9] and delayed-matching-to-sample [11] procedures Tolerance developed to the rate-decreasing effects of methsuximide in the present study, thus it appears that ethosuximide and methsuximide are similar in that their behavioral effects decrease with repeated exposure Interestingly, little or no tolerance develops to the anticonvulsant effects of these drugs when they are used clinically, therefore in clinical practice dosages are not characteristically increased over time [13]

The pharmacokinetics and biotransformation pathways of methsuximide in pigeons have not been evaluated and the mechanisms through which tolerance develops to its behavioral effects are unknown In mammals the drug is rapidly metabolized (the half-life is less than 2 hours) by various microsomal enzymes to the N-demethyl (2-methyl-2-phenylsuccinimide) and various parahydroxyphenyl derivatives The N-demethyl metabolite has anticonvulsant properties and a half-life of about 40 hours in humans [13]

A growing body of data suggests that the behavioral effects of anticonvulsants, like those of other drugs, depend upon how the behavior in question is maintained [8] Because of this, two agents may produce dissimilar effects under one assay, but not under another This is the case with methsuximide and ethosuximide Unfortunately, the neuropharmacological mechanisms that determine the behavioral effects of these drugs under diverse assays are unknown Although it is speculated on the basis of antiseizure activity that methsuximide has neuropharmacological actions different from or in addition to those of ethosuximide, the nature of these actions and their relation to ongoing behavior have not been determined [4,12]

ACKNOWLEDGEMENT

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