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# Convulsant Versus Typical Barbiturates: Effects on Locomotor Activity

ROCHELLE J DARNELL, TIMOTHY C McCLOSKEY AND RANDALL L COMMISSARIS[1]

*Department of Pharmaceutical Sciences, College of Pharmacy and AHP and Department of Psychiatry, School of Medicine, Wayne State University, Detroit, MI 48202*

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DARNELL, R J , T C McCLOSKEY AND R L COMMISSARIS *Convulsant versus typical barbiturates Effects on locomotor activity* PHARMACOL BIOCHEM BEHAV **24**(3) 727–731, 1986 — The present studies examined the effects of a typical (secobarbital) and a convulsant (cyclohexylideneethyl-5-barbituric acid [CHEB]) barbiturate on spontaneous locomotor activity in rats Administered alone, secobarbital produced a mild stimulation of activity at a low (2 5 mg/kg) dose, and a dose-dependent depression of locomotor activity at higher (5–20 mg/kg) doses Surprisingly, the convulsant barbiturate CHEB produced a depression of locomotor activity at all subconvulsant doses tested (2 5–20 mg/kg) IP administration of CHEB was also observed to produce abdominal muscle contractions (writhing) In a second experiment, it was found that the writhe-inducing compound para-phenyl-quinone (PPQ) did not affect locomotor activity, indicating that the depression of activity produced by CHEB was not secondary to its writhe-producing effects In a third experiment, the "barbiturate antagonist" potential of CHEB was examined Treatment with 10 mg/kg CHEB did not significantly alter the depression of locomotor activity produced by 10 mg/kg secobarbital These data suggest that (1) typical and convulsant barbiturates are not strict opposites in terms of all of their behavioral actions and (2) CHEB may not be effective as a "barbiturate antagonist "

Barbiturates CHEB Cyclohexylideneethyl-5-barbituric acid "Barbiturate antagonist" Locomotor Activity Secobarbital PPQ Writhing

BARBITURATES are non-selective depressants of the central nervous system They have a wide spectrum of actions including sedative-hypnotic, muscle relaxant, anxiolytic and, for most barbiturates, anti-convulsant properties [7] This spectrum of actions is similar to that of the benzodiazepines Since the introduction of the benzodiazepines, the barbiturates have not been used as extensively as they once were, primarily because of their relatively narrow therapeutic index

The mechanism(s) by which sedative-hypnotic agents produce their effects has been studied extensively over the last decade Perhaps the major breakthrough in this area has been the isolation and investigation of the benzodiazepine receptor and the GABA-benzodiazepine receptor complex ([18], see also review by [15]) The discovery of the specific benzodiazepine antagonist, Ro15-1788, and subsequent functional studies in rats employing the use of this compound, have provided clear and convincing evidence that most, if not all, of the effects of benzodiazepines are mediated through actions upon benzodiazepine receptors [9, 12, 13] In contrast, the behavioral effects in rats of the non-benzodiazepine sedative-hypnotics pentobarbital and methaqualone are not reversed by co-administration of the benzodiazepine antagonist Ro15-1788 [13]

It has been reported that barbiturates exert actions on the chloride ionophore within the GABA-benzodiazepine receptor complex ([14,16], see review by [15]) The barbiturate-induced increase in chloride permeability and resultant membrane hyperpolarization has been suggested to account for many of the behavioral actions of barbiturates. However, data addressing this hypothesis are lacking, principally because a barbiturate antagonist does not currently exist

Although an analogous "barbiturate antagonist" has not yet been identified, there do exist agents which are categorized as "atypical" or convulsant barbiturates [1–6, 8, 10, 11] Perhaps the most notable of these is cyclohexylideneethyl-5-barbituric acid (CHEB) Although this agent has been shown to be *pro-*, rather than *anti-*convulsant, the effects of this agent on the remaining aspects of the spectrum of barbiturate effects (sedative-hypnotic, anxiolytic) have not been reported Moreover, interaction studies examining the "barbiturate antagonist" potential of this agent have not been conducted

The present studies were designed (1) to determine the acute effects of the convulsant barbiturate CHEB (and the typical barbiturate secobarbital) on locomotor activity in rats and (2) to examine the possibility that CHEB might have potential as a "barbiturate antagonist "

[1]Requests for reprints should be addressed to Randall L Commissaris, Dept Pharmaceutical Sciences, College of Pharmacy and AHP, Wayne State University, Detroit, MI 48202

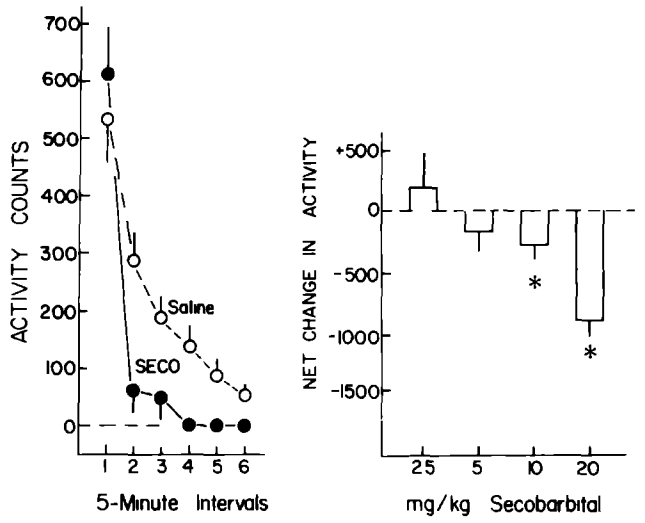


FIG 1 The effects of secobarbital on spontaneous locomotor activity in rats Left Panel Time course for the effects of 20 mg/kg secobarbital (filled circles) and saline (open circles) administration on locomotor activity Each symbol and vertical bar represents the mean±SEM for eight subjects Secobarbital significantly depressed activity relative to controls Right Panel Dose-dependent effects of secobarbital on locomotor activity Each column and vertical bar represents the mean±SEM net change in activity (secobarbital minus saline) for eight subjects Secobarbital tended to increase activity at the lowest dose employed (2 5 mg/kg), higher doses resulted in a dose-dependent depression of locomotor activity *$p<0$ 05 with respect to vehicle treatment, one-way ANOVA

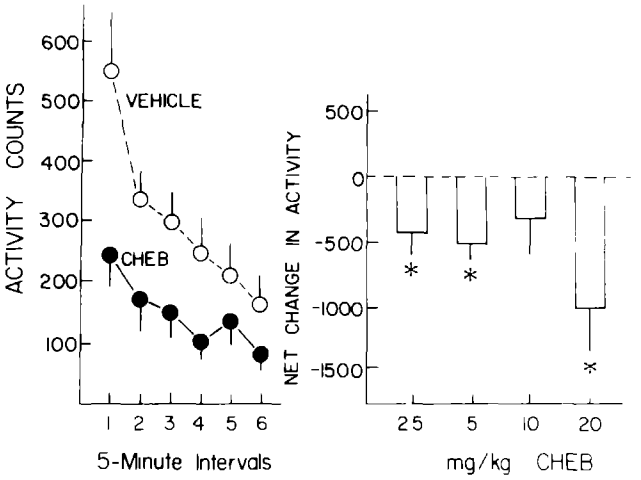


FIG 2 The effects of the convulsant barbiturate CHEB on locomotor activity Left Panel Time course for the effects of 20 mg/kg CHEB (filled circles) or vehicle (open circles) administration on locomotor activity Each symbol and vertical bar represents the mean±SEM for eight subjects CHEB significantly depressed locomotor activity relative to controls Right Panel Dose-dependent effects of CHEB on locomotor activity Each column and vertical bar represents the mean±SEM net change in activity for eight subjects CHEB administration resulted in a depression of locomotor activity at all doses tested, *$p<0$ 05 with respect to vehicle treatment, one-way ANOVA

## GENERAL METHOD

### *Subjects*

The subjects were male Sprague Dawley (Charles River, Inc , Portage, MI) rats weighing 225–250 g at the start of the experiments The subjects were housed in groups (four per cage) and were given food and water ad lib in a climate-controlled environment Lighting in the animal room was maintained on a 12 hr light 12 hr dark cycle (lights on 0600–1800 hr) Testing was conducted between 1000 and 1400 hr

### *Apparatus*

Locomotor activity was tested in a chamber (45×45×30 cm) with an 8×8 grid of infrared photocell activity emitters and detectors spaced 5 cm apart along the X and Y axes (Coulbourn Instrument Co , Lehigh Valley, PA) The apparatus was used to measure three kinds of activity linearly-directed, total (directed + non-directed) and vertical (rearings) The activity monitors were connected to a printer (Datalogger 8000-I, Coulbourn Instrument Co ) which was programmed to report accumulated activity counts at either 3 or 5 minute intervals for up to one hour, depending upon the particular experiment In the present studies, no treatment differentially affected total, vertical or directed locomotor activity, therefore, the effects of various treatments on directed activity only are presented in the present paper

### *Drugs*

Secobarbital sodium (Sigma Chemical Co , St Louis, MO) was prepared in 0.85 percent saline in doses from 2 5–20 mg/kg CHEB (courtesy of Dr Hal Downes, University of Oregon, Portland, OR) was prepared in a 0 5 percent cornstarch suspension in doses from 2 5–20 mg/kg All of these doses were below the threshold for convulsions produced by CHEB when administered IP in a cornstarch suspension IP administration of 40 mg/kg produced convulsions in approximately one third of the subjects examined Phenyl-para-quinone (PPQ, 0 02 percent solution [Sigma Chemical Co ]) was prepared in a 5 percent ethanol solution in saline Secobarbital and CHEB were administered in a volume of 1 0 ml/kg body weight PPQ was administered in a 5 ml constant volume All drugs were administered intraperitoneally All control subjects received appropriate vehicle injections

### *Statistical Analyses*

Cumulative activity counts over the test session were used for statistical analyses, the effects of single doses of drugs were compared to the appropriate control by one-way ANOVA with repeated measures The effects of CHEB treatment on secobarbital-induced depression of activity were assessed by two-way ANOVA with repeated measures

## EXPERIMENT 1 ACUTE EFFECTS OF SECOBARBITAL AND CHEB ON LOCOMOTOR ACTIVITY

### *Procedure*

Experiment 1 was designed to determine and compare the effects on spontaneous locomotor activity of a typical barbiturate, secobarbital, and a convulsant barbiturate, CHEB These experiments employed a standard "crossover" design which is described below On Test Day 1, half of the subjects received vehicle injection while the other half received a

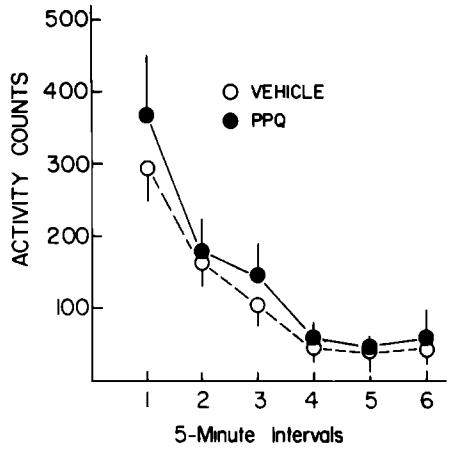


FIG 3 Time course for the effects of treatment with the writhe-inducing agent PPQ on locomotor activity Each symbol and vertical bar represents the mean±SEM obtained from eight subjects PPQ treatment (filled circles) had no effect on locomotor activity compared to vehicle-treated (open circles) controls

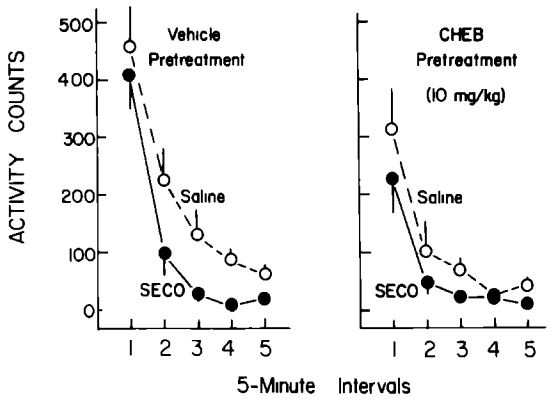


FIG 4 The effects of CHEB co-treatment on the depressant effects of secobarbital Time course for the effects of 10 mg/kg secobarbital (filled circles) or saline (open circles) administration on locomotor activity in CHEB (10 mg/kg, right panel)- or vehicle (left panel)-treated subjects Each symbol and vertical bar represents the mean±SEM obtained from 16 subjects Secobarbital significantly depressed locomotor activity relative to saline CHEB treatment did not significantly affect this secobarbital-induced depression of locomotor activity

dose of the particular drug under investigation One week later (Test Day 2) this procedure was repeated, except that the treatments were reversed Thus, each rat served as his own control with respect to drug versus vehicle injection Each dose of each drug was studied in a separate group of eight subjects In all test sessions, activity was recorded every 5 minutes for a 30-minute period starting immediately after injection

*Results*

The effects of secobarbital on locomotor activity are shown in Fig 1 The left panel of Fig 1 illustrates the time course for the effects of saline or 20 mg/kg secobarbital on locomotor activity Saline-treated subjects were very active in the first interval and displayed a progressive decrease in activity over the course of 30 minutes Treatment with 20 mg/kg secobarbital did not disrupt this habituation, but activity levels were depressed relative to saline-treated subjects at all time periods after the first interval

The right panel of Fig 1 illustrates the dose-dependent effects of secobarbital on locomotor activity There was a moderate stimulation relative to saline controls seen with the low dose of secobarbital (2 5 mg/kg), this effect was not statistically significant, $F(1,7)=4\ 31$, n s There was a depressant effect with the 5, $F(1,7)=3\ 22$, n s , 10, $F(1,7)=5\ 82$, $p<0\ 05$, and 20, $F(1,7)=13\ 62$, $p<0\ 01$, mg/kg doses, the intensity of this effect was dose-dependent

Figure 2 illustrates the effects of the convulsant barbiturate, CHEB, on locomotor activity The left panel illustrates the time course for the effects of 20 mg/kg CHEB or its vehicle (cornstarch) As can be seen, vehicle-treated subjects displayed a typical habituation curve CHEB-treated subjects were markedly depressed relative to controls throughout the test session, interestingly, this decrease in activity was particularly impressive during the first interval post-injection

The dose-response curve for the effects of CHEB on activity is shown in the right panel of Fig 2 As can be seen, CHEB produced a decrease in activity at all doses tested The CHEB-induced depression of locomotor activity was statistically significant for the 2 5, $F(1,7)=7\ 34$, $p<0\ 05$, 5, $F(1,7)=8\ 20$, $p<0\ 05$, and 20, $F(1,7)=13\ 56$, $p<0\ 01$, mg/kg doses, but not for the 10 mg/kg dose, $F(1,7)=5\ 20$, n s The magnitude of this depression was highest at the 20 mg/kg dose

## EXPERIMENT 2 WRITHING AND LOCOMOTOR ACTIVITY

An interesting observation associated with CHEB administration was the production of "writhing," or abdominal muscle contractions, with the IP administration of this compound This "writhing" was not produced by the CHEB vehicle and was similar in topography to the writhing produced by the administration of the local irritant phenyl-para-quinone (PPQ, [17]) Therefore, a second study was designed to evaluate the possible contribution of this writhing to the locomotor depressant effects observed with CHEB

*Procedure*

The present series of investigations were designed to examine the possible relationship between writhing *per se* and locomotor activity In this study, the locomotor effects of the writhe-inducing compound PPQ or its vehicle were determined in a group (N=8) of subjects, this study employed a standard "crossover" design (see Experiment 1) The PPQ dose employed in the present study, 0 02 percent in a 5 percent ethanol solution, has been demonstrated to produce a significant increase in writhing in our laboratory (unpublished data) and other laboratories [17]

*Results*

Figure 3 illustrates the effects of the peripherally-acting writhe-inducer PPQ or its vehicle on locomotor activity Treatment with a writhe-inducing dose of PPQ does not significantly affect locomotor activity, $F(1,7)<1$ 0, n s Therefore, it is unlikely that the decrease in locomotor activity produced by CHEB administration (Experiment 1) is secondary to its writhe-inducing effects

EXPERIMENT 3 CHEB AS A "BARBITURATE ANTAGONIST"

*Procedure*

The purpose of this experiment was to determine the "barbiturate antagonist" potential of the atypical barbiturate CHEB In this experiment subjects (n=16) were given each of four different treatments CHEB (10 mg/kg) + secobarbital (10 mg/kg), CHEB + saline, cornstarch + secobarbital or cornstarch + saline These 4 test sessions were balanced across subjects and were conducted at weekly intervals The secobarbital or saline treatments were administered 15 minutes, and the CHEB or cornstarch treatments 10 minutes prior to the start of testing Activity was monitored for 15 minutes in 3-minute intervals

*Results*

The results are shown in Fig 4 The left panel of Fig 4 illustrates the depressant effects of 10 mg/kg secobarbital relative to saline in cornstarch-treated subjects The right panel illustrates the effects of secobarbital versus saline in subjects treated with 10 mg/kg CHEB As expected, secobarbital treatment significantly reduced activity relative to saline-treated controls, $F(1,15)=12$ 54, $p<0$ 01 Again, CHEB treatment significantly decreased activity relative to cornstarch treatment, $F(1,15)=12$ 30, $p<0$ 01 CHEB treatment had a tendency to reduce the depressant actions of secobarbital, but this effect was not statistically significant, $F(1,15)=2$ 35, n s

GENERAL DISCUSSION

Secobarbital treatment produced an anticipated mild stimulation of activity at the lowest dose, and a dose-dependent depression of activity at higher doses Surprisingly, CHEB administration failed to increase activity at any of the doses employed Rather, CHEB administration resulted in a *decrease* in activity at all doses tested These similar effects of CHEB and secobarbital on locomotor activity are surprising in light of the opposite effects of typical and convulsant barbiturates on convulsive thresholds [1 2 8] Thus, these typical and convulsant barbiturates are not strict opposites in terms of their behavioral actions The locomotor effects of other convulsant barbiturates have not yet been examined Similarly, the effects of CHEB or other convulsant barbiturates on another behavioral aspect of the spectrum of typical barbiturate effects (i e , anti-anxiety actions) have not yet been investigated

The opposite effects of typical barbiturates and CHEB on seizure threshold and convulsive states [1, 2, 8], combined with the *similarities* in the effects of secobarbital and CHEB on locomotor activity, suggest that a somewhat different mechanism of action may mediate these two actions of CHEB

The results of Experiment 2 suggest that the writhing and the locomotor depressant effects of CHEB are independent actions, since PPQ treatment produces writhing similar to that seen with CHEB but has no depressant effect on locomotor activity Thus, it can be concluded that the writhing *per se* caused by CHEB administration is not responsible for the decreased activity observed with this agent

The mechanism for this CHEB-induced writhing remains undetermined Pretreatment with the anti-inflammatory agent aspirin (40 mg/kg) completely prevents PPQ-induced writhing, but appears to be considerably less effective in preventing CHEB-induced writhing (unpublished data), these data suggest that CHEB is not producing writhing via local irritant effects

In Experiment 3, it was shown that CHEB co-administration failed to significantly reduce the locomotor depressant effects of 10 mg/kg secobarbital This finding suggests that CHEB may not be effective as a "barbiturate antagonist" It should be noted, however, that the present studies employed only one dose of CHEB at a single pretreatment time, it is possible that more extensive dose and time course studies would provide a different result Moreover, the potential of other convulsant or atypical barbiturates to serve as "barbiturate antagonists" has not been explored to date

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