J.Pharmacol.Exper.Therap. 118, 153 (1956).

THE PHARMACOLOGIC ACTIVITY OF α-(4-PIPERIDYL)-BENZHYDROL HYDROCHLORIDE (AZACYCLONOL HYDROCHLORIDE);[1] AN ATARACTIVE AGENT[2]

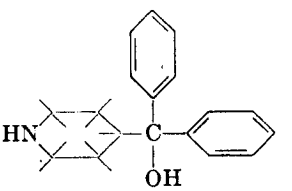
BARBARA B. BROWN, DONALD L. BRAUN AND ROBERT G. FELDMAN

Department of Pharmacology, Scientific Laboratories, The Wm. S. Merrell Co., Cincinnati 15, Ohio

Received for publication May 12, 1956

It was reported by Brown and Werner (1954) that the central stimulant pipradrol causes accelerated coordinated movements and behavioral changes of central origin. The 4-piperidyl isomer of pipradrol was subsequently studied and found to possess little observable pharmacologic activity except its ability to antagonize drug-induced coordinated hyperactivity. This unusual finding led to clinical trial of the 4-isomer in excited mental states. Recently Fabing (1955a, 1955b), Rinaldi *et al.*, (1955) and Proctor (1955) reported that the 4-isomer appears to have a specific effect in eliminating hallucinatory phenomena in acute schizophrenics. Fabing (1955c) suggested the descriptive word ataractic for drugs with this action.

The 4-isomer of pipradrol has the generic name of azacyclonol hydrochloride and is α-(4-piperidyl)-benzhydrol hydrochloride. The base has the following structure.



Azacyclonol hydrochloride is a white crystalline, odorless substance having a slightly bitter taste. It is soluble approximately 1 part to 100 parts of water.

METHODS. *Effects on coordinated activity of mice.* In order to quantify the mild degree of depressant activity induced by azacyclonol, the photocell counter technique of Dews (1953) was employed. Groups of 5 mice each are placed in small boxes having two plastic sides through which a light beam passes to a photoelectric cell. A counter in the circuit totals the number of times the mice cross the beam. In none of the experiments did any individual mouse show either a complete absence of activity or any sign of incoordinated behavior, unless specifically noted.

Activity counts were recorded at 15 minute intervals and totalled for the test period of 90 minutes. Drug administrations were made 15 minutes before placing the mice in the box unless otherwise specified. Control mice received saline or carboxymethyl cellulose

[1] Trade name, Frenquel.

[2] A preliminary report was given at the Federation Meetings in San Francisco (April, 1955).

TABLE 1

Acute toxicity values of azacyclonol and pipradrol for mice

Compound	LD_{50} Values and Standard Errors*			
	Intravenous	Intraperitoneal	Subcutaneous	Oral
	mgm./kgm.	*mgm./kgm.*	*mgm./kgm.*	*mgm./kgm.*
Azacyclonol	177 ± 12	220 ± 31	355 ± 28	650 ± 39
Pipradrol	43 ± 3.1	94 ± 8	147 ± 8	120 ± 8

* Estimated by the method of Miller and Tainter (1944).

vehicle injections at the same time. Five groups or more were employed at each dose level in determining the dose-effect curve for azacyclonol.

Effect on duration of hexobarbital sleeping time in mice. A dose of 100 mgm./kgm. of hexobarbital sodium intraperitoneally caused mean sleeping times of 26, 33, 35 and 39 minutes in four different experiments employing groups of 12 male mice each. Sleeping time was judged from loss of righting reflex to regaining the righting reflex. The righting reflex was considered returned when the mouse righted itself within thirty seconds after being placed on its back following occurrence of spontaneous righting. Each series of experiments with controls were done on the same day.

Respiratory and cardiovascular effects. Azacyclonol was administered intravenously at a rate of 40 mgm. per minute to dogs anesthetized with chloralose. Blood pressure was recorded from the femoral artery, respiration was recorded by means of an inspirometer, and a lead II electrocardiogram was taken.

RESULTS. *Acute toxicity.* Estimates of the acute toxicity of azacyclonol hydrochloride were made following several routes of administration to mice. Toxicity values are compared to those for pipradrol in table 1.

Azacyclonol has a low order of toxicity following all four routes of administration, and it is of lower toxicity than pipradrol. Lethal and near-lethal doses caused convulsions. Deaths occurred between twenty minutes and four hours after administration of the drug.

Effects and signs of toxicity of azacyclonol varied with the species. In mice, small to moderate doses caused a mild depression which was characterized only by decreased spontaneous activity and completely normal locomotor responses to stimulation. In rats, doses as low as 86 mgm./kgm. subcutaneously (about ten per cent of the LD_{50}) produced a peculiar flaccid paralysis of the hind legs, depressed spontaneous activity, and increased responsiveness to auditory stimuli. Lethal and near-lethal doses caused loss of control of hind legs and generalized tremors with death occurring without overt convulsions.

The oral administration of doses of 25 and 50 mgm./kgm. of azacyclonol to dogs and cats caused increased irritability, occasional tremors and inability to rest. Doses of 100 mgm./kgm. orally caused the dogs to be in constant motion with curious rapid alteration of front foot placing which is also a characteristic of pipradrol toxicity in dogs.

Single doses as high as 160 mgm./kgm. orally in monkeys caused no observable changes in behavior and no signs of toxicity.

Effects on coordinated activity of mice. Results of these studies are graphed in the lower part of figure 1. Doses of 20, 40 and 60 per cent of the LD_{50} (71, 142

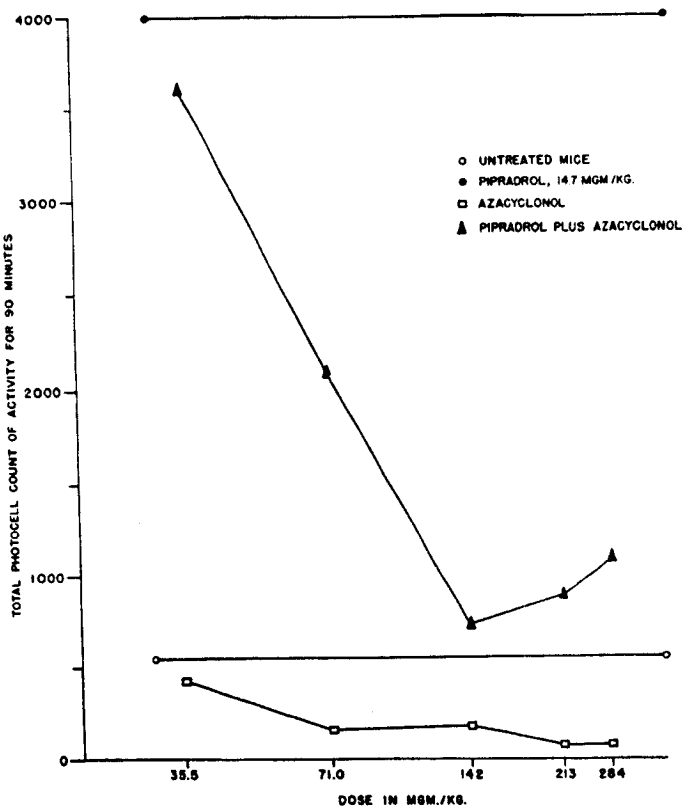


FIG. 1. The effect of azacyclonol on spontaneous activity and on hyperactivity induced by pipradrol as measured by the photocell counter technique in mice.

and 213 mgm./kgm.) of azacyclonol reduced the activity of mice by more than 50 per cent. A dose of 80 per cent of the LD_{50} is similarly effective but occasional brief tremors could be observed during the activity measurements.

Azacyclonol-induced depression occurred with all three routes of administration (table 2). The mice were placed in the activity boxes immediately after intravenous and subcutaneous administrations, using aqueous solution, and 15 minutes after oral administration of the drug suspended in 1 per cent carboxymethyl cellulose.

Antagonism of drug-induced hyperactive states in mice. The effect of azacyclonol in stimulated states was first studied by determining its antagonism of coordinated hyperactivity induced by pipradrol. Groups of mice were administered an optimally stimulating dose of pipradrol, 14.7 mgm./kgm., subcutaneously (Brown and Werner 1954) simultaneously with the subcutaneous injection of various doses of azacyclonol. Figure 1 shows that a dose of 20 per cent of the

TABLE 2

Maximally depressant effects of azacyclonol by various routes of administration to mice

Dose	Route	No. Groups	Average Photocell Counts for Time Intervals in Minutes						Average Total for 90 Min.	Reduction in Activity
			15	30	45	60	75	90		
mgm./kgm.										*per cent*
93 (60% LD_{50})	I.V.	2	23	22	6	6	12	23	92	82
213 (60% LD_{50})	Subcut.	4	33	12	7	8	6	4	70	86
Control	I.V. and subcut.	9	162	105	83	76	53	38	517 ± 82	
520 (80% LD_{50})	Oral	2	56	5	6	10	12	25	114	70
Control	Oral	10	160	89	52	44	23	12	381 ± 39	

LD_{50} of azacyclonol (71 mgm./kgm.) decreased the pipradrol-induced hyperactivity by about one-half, and twice this dose almost completely prevented any increase above normal activity. The maximal degree of antagonism varied, however, between fifty and ninety per cent reduction of pipradrol-induced hyperactivity. The cause of this variation has not been uncovered. Mice treated with 14.7 mgm./kgm. of pipradrol will remain active for twelve or more hours. Mice receiving pipradrol combined with 142 mgm./kgm. of azacyclonol showed no hyperactivity for a similar period. Larger doses of azacyclonol are less effective in neutralizing the induced activity presumably because stimulating doses of azacyclonol are being approached as evidenced by the occurrence of occasional tremors at the 80 per cent dose level combined with pipradrol.

The effect of azacyclonol on degree of coordinated activity induced by other centrally stimulating substances was evaluated by the same test procedure and is recorded in table 3. The maximally effective dose of azacyclonol in antagonizing pipradrol-induced activity, 142 mgm./kgm. (40 per cent of the LD_{50}) subcutaneously, was used in these experiments. This dose caused a 60 per cent reduction in the hyperactivity induced by the three agents, d-amphetamine, morphine and cocaine. Larger doses of azacyclonol were no more effective in neutralizing the stimulating effects of these agents. The intravenous effectiveness of azacyclonol is also indicated in table 3.

Effect on duration of hexobarbital sleeping time in mice. The subcutaneous injection of azacyclonol in doses of 17 to 142 mgm./kgm. (5 to 40 per cent of LD_{50}) 15 minutes before the intraperitoneal injection of hexobarbital increased sleeping time moderately in all instances (table 4).

Results in table 5 show that prolongation of hexobarbital sleeping time is also obtained when azacyclonol is administered 4 hours prior to the barbiturate but the effect of azacyclonol has disappeared in 24 hours.

Brodie (1955) has reported that reserpine prolongs hexobarbital sleeping time in mice and that 10 mgm./kgm. of LSD one hour before antagonizes the effect. Results in table 5 indicate that prior administration of LSD does not shorten the increased sleeping time caused by azacyclonol.

In additional experiments azacyclonol was injected intravenously in mice fully recovered from the hexobarbital hypnosis. Hypnosis was re-induced in

TABLE 3

Antagonism by azacyclonol of coordinated hyperactivity induced in mice by several stimulants

Stimulant	Dose	Route	Azacyclonol		Average Photocell Count 90 Min.*	Reduction of Activity
			Dose	Route		
	mgm./kgm.		*mgm./kgm.*			*per cent*
			—		517	
			93	I.V.	92	82
			142	Subcu.	154	70
Pipradrol·HCl	14.7	Subcu.	—	—	4016	
Pipradrol·HCl	14.7	Subcu.	93	I.V.	1322	67
Pipradrol·HCl	14.7	Subcu.	142	Subcu.	1091	73
d-amphetamine·SO_4	9.3	Subcu.	—		3098	
d-amphetamine·SO_4	9.3	Subcu.	142	Subcu.	1312	58
Morphine·SO_4	40	Subcu.	—		1864	
Morphine·SO_4	40	Subcu.	142	Subcu.	728	60
Cocaine·HCl	20	Subcu.			2059	
Cocaine·HCl	20	Subcu.	142	Subcu.	764	62

* Average of 10 groups for control value, 5 groups for each pipradrol and azacyclonol determination, and 3 groups for remainder of the studies.

TABLE 4

Effect of azacyclonol subcutaneously on duration of hypnosis induced by 100 mgm./kgm. of hexobarbital sodium intraperitoneally in mice

Dose of Azacyclonol	Hexobarbital Alone	Azocyclonol + Hexobarbital	Average Increase
	Av. sleeping time ± S.E.	Av. sleeping time ± S.E.	
mgm./kgm.	*minutes*	*minutes*	*per cent*
17	35 ± 2 (12)	48 ± 3.8 (12)	37
35.5	33 ± 3.6 (12)	54 ± 3.8 (12)	63
71	33 ± 3.6 (12)	66 ± 3.2 (12)	100
142	26 ± 2.6 (12)	56 ± 6.6 (12)	115

TABLE 5

Effect of azacyclonol intraperitoneally on duration of hexobarbital hypnosis in mice at different time intervals and the influence of LSD-25

Drug	I.P. Dose	Time Given Before Hexobarbital	Drug	I.P. Dose	LSD-25 1 hr. Before Hexobarbital I.P.	Average Sleeping Time ± S.E.
	mgm/kgm.	*hours*		*mgm./kgm.*	*mgm./kgm.*	
			Hexobarbital	100		39 ± 3.8
Azacyclonol	44	0.25	Hexobarbital	100		62 ± 3.1
Azacyclonol	44	4	Hexobarbital	100		78 ± 6
Azacyclonol	44	0.25	Hexobarbital	100	10	73 ± 5.3
Azacyclonol	44	24	Hexobarbital	100		32 ± 4

TABLE 6

Re-induction of hypnosis by azacyclonol intravenously following spontaneous arousal of mice from hexobarbital hypnosis

Hexobarbital 100 mgm./kgm. I.P.	Drug	Intravenous Dose	Incidence of Re-hypnosis	Av. Additional Sleeping Time
Av. sleeping time min.		*mgm./kgm.*		*minutes*
18	azacyclonol	70	5/6	12
32	azacyclonol	105	4/6	26

the majority of mice, and the second sleeping time was approximately as long as the original hypnosis (table 6).

Morphine stimulation in cats. The effect of azacyclonol on morphine stimulation and toxicity was studied by injecting 12 cats with 25 mgm./kgm. of morphine sulfate subcutaneously. Six of the cats were pre-treated by the oral administration of azacyclonol in a dose of 5 mgm./kgm. orally for 5 days. This dosage caused no change in behavior or activity of the cats. All of the untreated cats convulsed within two to four hours and 5 of the 6 died. In contrast, of the 6 azacyclonol treated cats, 1 cat convulsed and died. The other 5 cats showed only a mild degree of stimulation lasting for 3 to 4 hours.

Respiratory and cardiovascular effects in dogs. Doses of 16 mgm./kgm. caused a variable blood pressure response, being either slightly pressor or slightly depressor. Effects on heart rate and respiration were slight and variable. Amplitude of the T wave of the ECG was increased. Doses of 32 mgm./kgm. generally caused a marked fall in blood pressure and a small increase in heart rate. The QRS complex showed a tendency to inversion and the T wave was of considerable amplitude. The respiratory rate was significantly increased concomitant with the blood pressure fall. Lethal doses of about 45 mgm./kgm. produced a further exaggeration of the ECG changes suggesting ventricular anoxia, notably an apparent idioventricular rhythm with loss of the P wave and inversion of the QRS complex. In one dog ventricular tachycardia occurred.

LDS antagonism in man. On August 5, 1955, 100 microgm. of LSD-25 were administered orally to two subjects to determine onset of LSD antagonism by azacyclonol.[3]

Subject 1, a scholastically brillant but somewhat emotionally unstable 21 year old male responded to LSD within thirty minutes with inappropriate grinning gradually changing to giggling and loud laughter both in the presence and absence of the observers. The laughter became frequent and uncontrollable, and the subject became completely incapable of conversation. At the end of the experiment the subject reported an initial nausea followed by inability to control his laughter, which increased with all types of stimulation. He said that he had experienced a loss of will and that he could not respond physically to orders to sit, walk and stand (he actually did not cooperate with requests during the experiment). He reported seeing undulating faces and weird images on the floor.

[3] Experiments carried out in cooperation with Dr. H. D. Fabing, Christ Hospital, Cincinnati, Ohio.

This state continued for 3 hours at which time 100 mgm. of azacyclonol was injected intravenously.

Immediately after injection of azacyclonol, the subject suddenly sprawled in the chair, laughter ceased, and he was able to answer questions. His subsequent report stated that he became suddenly relaxed and very tired, that he returned to reality, images disappeared and he was able to control his laughter. He said he felt an enormous relief by the disappearance of the visual and auditory distortions, and that he regained his will.

Subject 2 is a highly intelligent, sensitive, artistic and well-adjusted 25 year old male. The first observable reaction to 100 microgm. LSD was crying which he said was due to a depression. He gradually became withdrawn but upon questioning he discussed his reactions adequately. He became somewhat disoriented in space and saw colored geometric designs. Two hours after LSD he had become communicative and then loquacious. He offered extensive philosophic comments on a variety of subjects and was primarily concerned with his *raison d'être*. He was quite anxious about his inability to express the myriad of thoughts in his mind. Asked to write his thought content, he scribbled in all directions on the paper, using half sentences and interjections.

The intravenous injection of 100 mgm. of azacyclonol 3½ hours after the LSD had no immediate effect, but within thirty minutes he appeared more relaxed and comfortable with no outward signs of anxiety. His flow of conversation diminished markedly over the next hour. At that time the writing of his thought content was accomplished in a well-organized, logical and neat manner. He later reported that after azacyclonol he became relaxed, thoughts came clearer, and slower, and that he felt as well as before the LSD.

On August 27, 1955 another experiment was conducted for which subjects 1 and 2 returned for a second LSD-azacyclonol experience but were given plain water instead of LSD. Four additional subjects were each given 100 microgm. of LSD in water. All of the four additional subjects developed moderate to severe symptoms of LSD effects whereas subjects 1 and 2, though expectant, experienced no subjective changes whatever. Three of the 4 LSD subjects received 100 mgm. of azacyclonol intravenously at the height of their reactions. Two of these were promptly relieved of the drug-induced psychosis whereas the third subject stated that no change in his subjective state occurred although "blind" observers noted a rapid disappearance of facial tenseness, decreased agitation and increased ability to communicate. The fourth subject received saline intravenously and no change in LSD symptoms occurred either subjectively or objectively over a subsequent 4 hour period.

Discussion. The compound α-(4-piperidyl)-benzhydrol hydrochloride (azacyclonol) possesses a mixture of central actions. Its mild depressant effect predominates over a wide dose range in mice and rats, whereas its stimulant effect predominates in cats and dogs. Monkeys exhibit no changes in general activity after oral administration of large doses.

The depression of activity induced by azacyclonol in mice is so mild that it can be demonstrated only by measurements of frequency of spontaneous move-

ment. Nevertheless, azacyclonol is capable of antagonizing to a marked degree coordinated hyperactivity induced by a variety of stimulants in mice and morphine-induced stimulation in cats.

The depressant component of azacyclonol can also be demonstrated by its effect in prolonging hexobarbital hypnosis. The fact that the hypnosis can be re-induced by intravenous azacyclonol suggests that its re-inforcement of hypnosis is not a result of interference with metabolism of the barbiturate.

The failure of LSD to affect the increase of hexobarbital sleeping time caused by azacyclonol does not necessarily mean that azacyclonol lacks LSD-antagonistic activity. Rinaldi and Himwich (1955) have demonstrated that azacyclonol corrects the cerebral electrographic changes produced by LSD in the rabbit. Such findings tend to corroborate clinical findings that the anti-LSD action of azacyclonol is limited to mental phenomena while not affecting the viscero-sympathetic component of the LSD-reaction (Fabing, 1955b).

The specificity of azacyclonol for acutely occurring confusional states has been demonstrated in profound LSD-induced psychoses (see above; Fabing, 1955d) as well as in acute schizophrenia. The ataractic effect also occurs in post-operative confusional states (Fabing, 1955c) and in other drug-induced psychoses (Ayd, 1955).

It is difficult to correlate the clinical effect of azacyclonol with either depressant or stimulant phases of its activity in animals. Neither schizophrenics nor LSD subjects show or report any changes in either physical or mental activity levels except those resulting from relief from confusion and the consequent regained ability to concentrate. The characteristic action of azacyclonol in an LSD-induced psychotic state is cessation of rush of unrelated thoughts, ideas, and even visual distortions with replacement by the usual level of thought association and perceptual relations. These changes may occur within minutes following intravenous administration. Similar changes appear to occur in certain hallucinating schizophrenics although an interval of 4 to 48 hours is required before the confusional state is eliminated.

SUMMARY

The compound α-(4-piperidyl)-benzhydrol hydrochloride, azacyclonol, causes depressed activity in mice and rats when small to moderate doses are administered but causes stimulation in large doses. Cats and dogs respond to azacyclonol only by stimulation.

Azacyclonol antagonizes increased coordination activity in mice induced by pipradrol, amphetamine, morphine and cocaine, and it antagonizes morphine-induced stimulation in cats.

Hexobarbital hypnosis is prolonged by azacyclonol, and can be re-induced by azacyclonol after the mice are fully awake.

The intravenous injections of azacyclonol in subjects with well-developed LSD-induced psychoses frequently caused prompt relief of the mental symptomatology.

REFERENCES

AYD, F., JR.: Am. Psychiat. Assoc., Midwest Regional Research Conference, Galesburg, Ill., September 16, 1955.
BROWN, B. B., AND WERNER, H. W.: THIS JOURNAL, **110:** 180, 1954.
DEWS, P.: Brit. J. Pharmacol., **8:** 46, 1953.
FABING, H. D.: Dis. Nerv. System, **16:** 3, 1955a.
FABING, H. D.: Neurology, **5:** 319, 1955b.
FABING, H. D.: J. Am. Med. Assoc., **158:** 1461, 1955c.
FABING, H. D.: Science, **121:** 208, 1955d.
MILLER, L. C., AND TAINTER, M. L.: Proc. Soc. Exper. Biol. Med., **57:** 261, 1944.
PROCTOR, R. C., AND ODLAND, T.: Dis. Nerv. System, **17:** 25, 1956.
RINALDI, G., RUDY, L. H., AND HIMWICH, H. E.: Am. J. Psychiat., **112:** 343, 1955.
RINALDI, F., AND HIMWICH, H. E.: Science, **122:** 198, 1955.
SHORE, P. A., SILVER, S. L., AND BRODIE, B. B.: Science, **122:** 284, 1955.