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PYSCHO-SEDATIVE PROPERTIES OF THREE INDOLYL-ETHYL-PIPERAZINE DERIVATIVES

BY

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The therapeutic success of chlorpromazine and reserpine in the symptomatic management of various forms of mental illness coupled with the frequent occurrence of undesirable side-effects with their prolonged use has stimulated a continuing search for better and safer drugs with a greater degree of specificity of action. A series of 4-aryl-1-(indolylalkyl)-piperazines synthesized by Archer, Wylie, Harris, Lewis, Schulenberg, Bell, Kullnig & Arnold (1962) was observed to possess sedative and tranquillizing properties in laboratory animals. The present studies are concerned with some neurophysiological and behavioural effects of three compounds belonging to this chemical series: Win 18,501–2; 1-[2-(5,6-dimethoxy-2-methylindol-3-yl)ethyl]-4-phenylpiperazine. Win 18,437; 1-[2-(2-methyl-indol-3-yl)ethyl]-4-phenylpiperazine. Solypertine tartrate (Win 18,413–2); 7-[2-(4-*o*-methoxyphenylpiperazine-1-yl)ethyl]-5*H*-1,3-dioxolo[4,5-*f*]indole tartrate; 1-(2-anisyl)-4-[2-(5,6-methylenedioxy-3-indolyl)ethyl]piperazine tartrate.

METHODS

Chlorpromazine was used for comparison in all the tests. The drugs were administered intraperitoneally as freshly prepared aqueous or saline solutions. The three Win compounds, due to their low solubility in water, were first dissolved in a small amount of lactic acid (0.02 to 0.10 ml. of 85.5% lactic acid per 20.0 mg of base).

White CF1 male mice, weighing 18 to 30 g, were used for the following tests: 24-hr LD50 was determined and potentiation of hexobarbitone sleeping time tested according to the method of Brown (1957). Hypothermic activity was observed by recording the rectal temperature with a probe tele-thermometer for 2 hr before injecting the drugs and then every 15 min for 6 hr. Protection against amphetamine toxicity in grouped and isolated mice was tested, using a technique modified from Burn & Hobbs (1958).

CD male rats (220 to 350 g), trained to avoid electric shocks (115 V) on presentation of an auditory signal for 5 sec, were used to study the effect of the drugs on the conditioned avoidance response (Cook & Weidley, 1957).

Female cats with chronically implanted electrodes were used to study the effect of the drugs on the spontaneous and evoked electrical activity of the brain. Both mono- and bi-polar recordings were taken. The electrical activity of the cortical (right and left median suprasylvian cortex) and the subcortical regions (caudate nucleus, nuclei centrum medianum and centralis lateralis of the thalamus, dorsal hippocampus, amygdalae and midbrain reticular formation) was recorded, using an eight-channel Offner-type D Electro-, encephalograph. Effects on the recruiting response to low-frequency (6 per sec; 1 msec) stimulation of the intralaminar thalamic nuclei (Dempsey & Morison, 1942) and on the arousal response to direct stimulation

(150 per sec; 1 msec) of the reticular formation (Moruzzi & Magoun, 1949) were also studied. The sites of all subcortical electrodes were subsequently verified.

Results were analysed statistically where appropriate, using the method of Litchfield & Wilcoxon (1949) or the *t*-test for significance.

RESULTS

Acute toxicity. Results of the acute toxicity study (Table 1) indicate the three Win compounds to be 1.5- to 3.0-times as toxic as chlorpromazine on intraperitoneal administration to mice. Qualitatively similar signs of neurotoxicity were observed with the Win compounds: catalepsy, ptosis, lachrimation, loss of pinna reflex, ataxia, loss of righting reflex, respiratory depression and clonic convulsions.

TABLE 1

ACUTE INTRAPERITONEAL TOXICITY IN MICE

Values are means with ranges in parentheses

	LD50 (mg/kg)	LD50 (mM/kg)	Slope of regression line
Chlorpromazine	244·4 (230·5–259·2)	0·766 (0·723–0·813)	1·12 (1·00–1·25)
Win 18,501–2	154·0 (140·0–169·4)	0·396 (0·368–0·446)	1·21 (0·89–1·63)
Win 18,437	157·2 (138·2–177·8)	0·495 (0·435–0·560)	1·24 (1·05–1·46)
Win 18,413–2	81·5 (72·8– 92·0)	0·214 (0·191–0·242)	1·18 (1·08–1·28)

TABLE 2

HEXOBARBITONE SLEEPING TIME IN MICE

Values for sleeping time are means and standard errors. N.S.= Not significant. Controls received only hexobarbitone and the solvent for the other drugs

Treatment	Sleeping time (min)	Relative sleeping time	*P*
Controls	22·55± 3·76	—	—
Chlorpromazine			
Controls	22·00± 2·03	1·00	
1 mg/kg	40·05± 8·01	1·84	0·05
2 mg/kg	45·70± 8·80	2·07	0·02
5 mg/kg	91·15±13·41	4·14	0·01
10 mg/kg	119·22± 7·92	5·41	0·01
Win 18,501–2			
Controls	41·15± 2·76	1·00	
1 mg/kg	52·45± 4·73	1·27	N.S.
2 mg/kg	62·75± 8·72	1·52	0·05
5 mg/kg	103·75±11·95	2·52	0·01
10 mg/kg	160·20±12·66	3·89	0·01
Win 18,437			
Controls	46·80± 3·27	1·00	
1 mg/kg	62·85± 6·76	1·34	0·05
2 mg/kg	80·85± 7·65	1·72	0·01
5 mg/kg	108·10± 5·12	2·30	0·01
10 mg/kg	130·10± 8·20	2·77	0·01
Win 18,413–2			
Controls	38·30± 4·83	1·00	
1 mg/kg	39·15± 4·07	1·02	N.S.
2 mg/kg	78·55± 7·28	2·05	0·01
5 mg/kg	106·30± 7·92	2·77	0·01
10 mg/kg	156·90± 7·48	4·09	0·01

TABLE 3
HYPOTHERMIC ACTIVITY IN MICE
Values are means and standard errors

Treatment	Maximum fall in body temperature (°C)
Controls	
Untreated	0·85±0·37
Saline	1·32±0·45
Lactic acid	1·13±0·21
Chlorpromazine	
5 mg/kg	5·43±0·39
10 mg/kg	7·50±0·44
Win 18,501–2	
5 mg/kg	6·73±0·69
10 mg/kg	7·30±0·72
Win 18,437	
5 mg/kg	5·72±0·71
10 mg/kg	5·76±1·26
Win 18,413–2	
5 mg/kg	5·88±0·59
10 mg/kg	6·01±0·72

TABLE 4
PROTECTION AGAINST AMPHETAMINE TOXICITY IN GROUPED MICE
Values are the percentage of mice protected

Dose (mg/kg)	Mice (%) protected after			
	Chlorpromazine	Win 18,501–2	Win 18,437	Win 18,413–2
Controls	0·0	0·0	0·0	0·0
0·5	50·0	50·0	0·0	33·3
1·0	100·0	83·3	50·0	66·6
2·0	100·0	100·0	83·0	100·0
4·0	100·0	100·0	100·0	100·0
8·0	100·0	100·0	100·0	100·0

TABLE 5
CONDITIONED AVOIDANCE RESPONSE IN RATS
Values are means with ranges in parentheses

Drug	ED50 (mg/kg)	ED50 (mM/kg)	Slope of regression line
Chlorpromazine	5·18 (3·95– 6·78)	0·016 (0·012–0·021)	1·71 (1·27–2·29)
Win 18,501–2	5·30 (3·76– 8·08)	0·014 (0·009–0·021)	2·42 (1·51–3·87)
Win 18,437	16·00 (12·80–20·00)	0·050 (0·040–0·062)	1·90 (1·26–2·85)
Win 18,413–2	8·55 (7·24–10·09)	0·022 (0·019–0·026)	1·47 (1·22–1·77)

Hexobarbitone sleeping time. Hexobarbitone sleeping time (Table 2) was potentiated by all four compounds. Although there is little significant difference between the three Win compounds, they appear to be somewhat weaker than chlorpromazine in this test. Lactic acid, in the amounts used to dissolve the Win compounds, itself significantly potentiated the hexobarbitone sleeping time.

Hypothermic activity. The three Win compounds showed hypothermic activity to the same degree as chlorpromazine (Table 3). Restraining the animals alone resulted in a drop of 2 to 3° C in body temperature, but the temperature became stabilized after 1 to 2 hr of confinement. The maximum fall in body temperature occurred between 1 to 2 hr after administration of the Win compounds and 2 to 3 hr after chlorpromazine, with recovery still not complete at 6 hr.

Amphetamine toxicity in aggregated and single mice. The LD50s of amphetamine sulphate in the grouped and the single mice were 10.2 and 144.0 mg/kg respectively. All four drugs effectively protected the grouped mice from amphetamine toxicity in doses of 0.5 to 2.0 mg/kg (Table 4). Little or no protection was observed in the single mice.

Conditioned avoidance response. All four drugs selectively blocked the conditioned avoidance response in rats (Table 5). Of the three Win compounds, Win 18,501–2 was

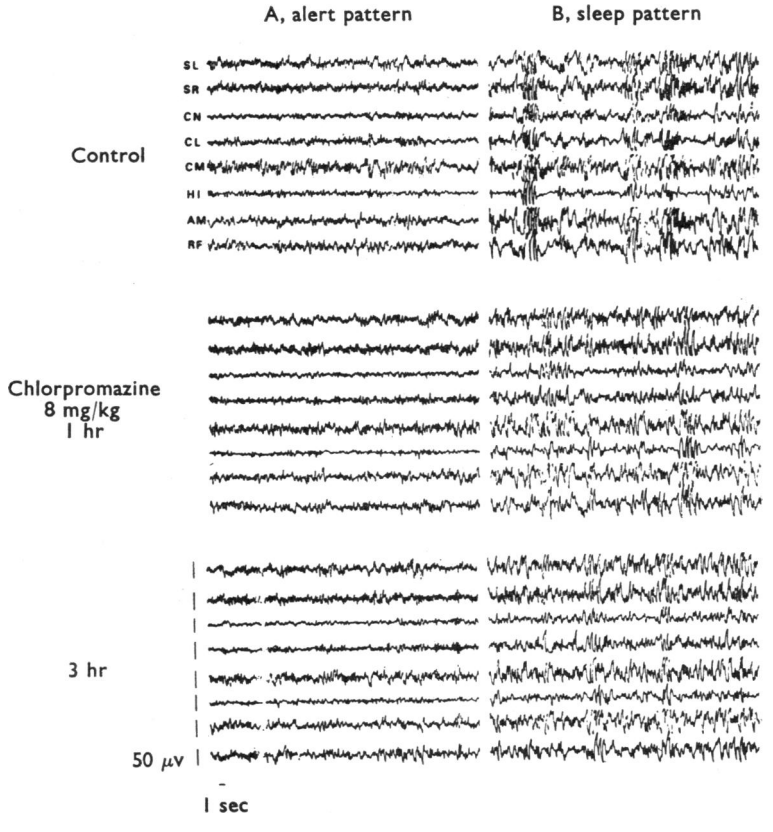

Fig. 1. The effect of chlorpromazine on the spontaneous electroencephalogram of the cat. Spontaneous brain activity before and after 8 mg/kg of chlorpromazine, intraperitoneally. Column A shows an alert pattern, while B shows a sleep pattern. Symbols are: SL, median suprasylvian cortex left; SR, median suprasylvian cortex right; CN, caudate nucleus; CL, nucleus centralis lateralis; CM, nucleus centralis medialis; HI, hippocampus; AM, amygdala; RF, reticular formation. Calibrations, 50 μV and 1 sec.

equipotent with chlorpromazine, whereas Win 18,437 was three times weaker and Win 18,413–2 showed intermediate activity. The peak effect was observed at 1 hr after the administration of the Win compounds and at 2 hr after chlorpromazine injection. No effect on the escape response was observed with Win 18,437 in doses up to 30 mg/kg which blocked 80% of the avoidance responses. The other three compounds showed similar relative effects on the two responses, blocking 10 to 20% of the escape responses in doses which abolished 80 to 90% of the avoidance responses.

Spontaneous and evoked electrical activity of the brain. The three Win compounds, in doses of 4 and 8 mg/kg, caused behavioural depression and apathy in the cats. The effects on behavioural sleep were more variable and ranged from a complete lack of sleep in one animal to increased drowsiness and excessive sleep activity in another during the 6-hr period of study. This was also true for chlorpromazine. All four drugs produced moderate to severe ataxia in the cats in the doses tested.

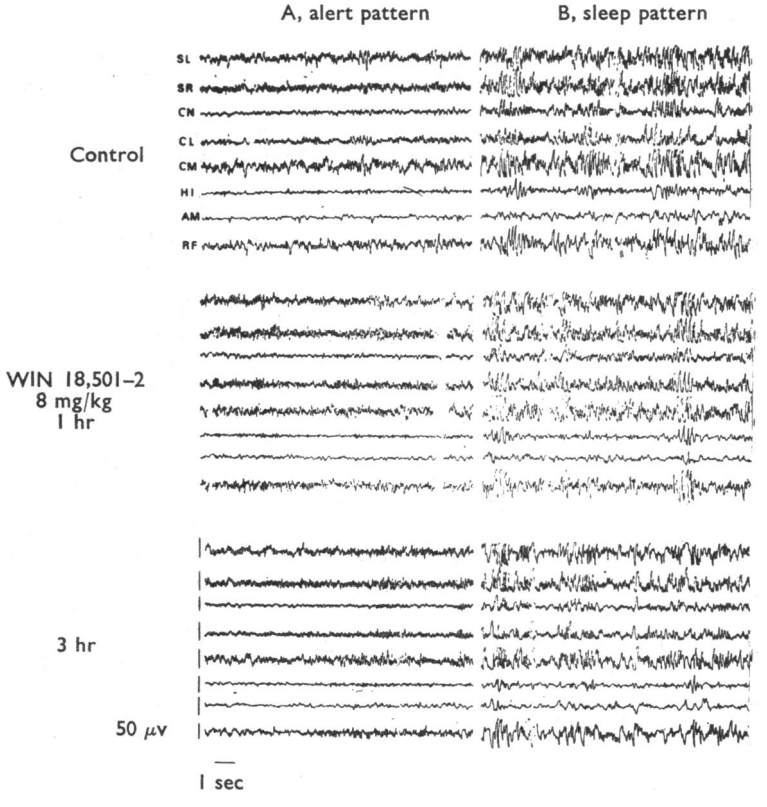

Fig. 2. The effect of Win 18,501–2 on the spontaneous electroencephalogram of the cat. Spontaneous brain activity before and after 8 mg/kg of Win 18,501–2, intraperitoneally. Column A shows an alert pattern, while B shows a sleep pattern. Symbols are: SL, median suprasylvian cortex left; SR, median suprasylvian cortex right; CN, caudate nucleus; CL, nucleus centralis lateralis; CM, nucleus centralis medialis; HI, hippocampus; AM, amygdala; RF, reticular formation. Calibrations, 50 μV and 1 sec.

There was a tendency for low-voltage fast activity to predominate in the spontaneous electroencephalogram of quietly resting awake animals after the Win compounds. However, no consistent changes in the spontaneous electrical activity were observed with all four drugs in doses up to 8 mg/kg (Figs. 1 and 2).

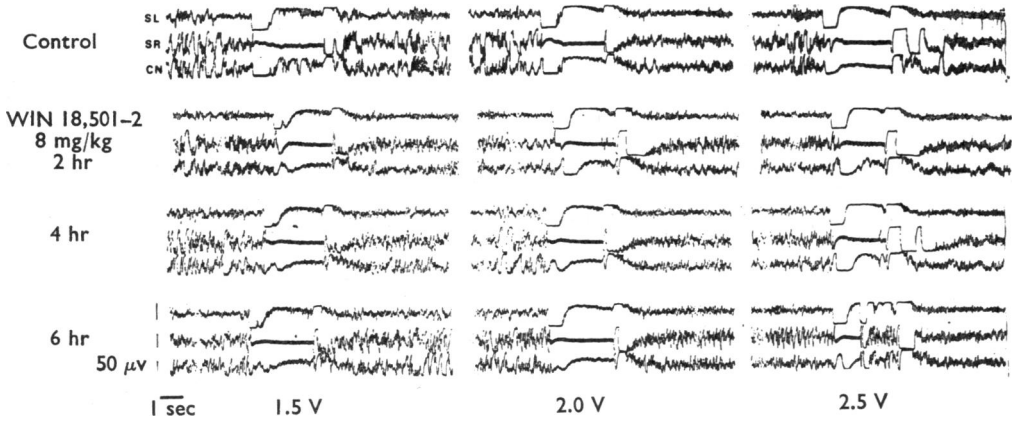

Fig. 3. The effect of Win 18,501-2 on the arousal thresholds in the cat. Electroencephalogram and behavioural arousal thresholds elicited by direct stimulation of the reticular formation before and after 8 mg/kg of Win 18,501-2, intraperitoneally. Stimulation was during the periods indicated by horizontal bars, at 1.5, 2.0 and 2.5 V for the three columns respectively. The last column shows behavioural arousal. Symbols are: SL, median suprasylvian cortex left; SR, median suprasylvian cortex right; CN, caudate nucleus. Calibrations, 50μV and 1 sec.

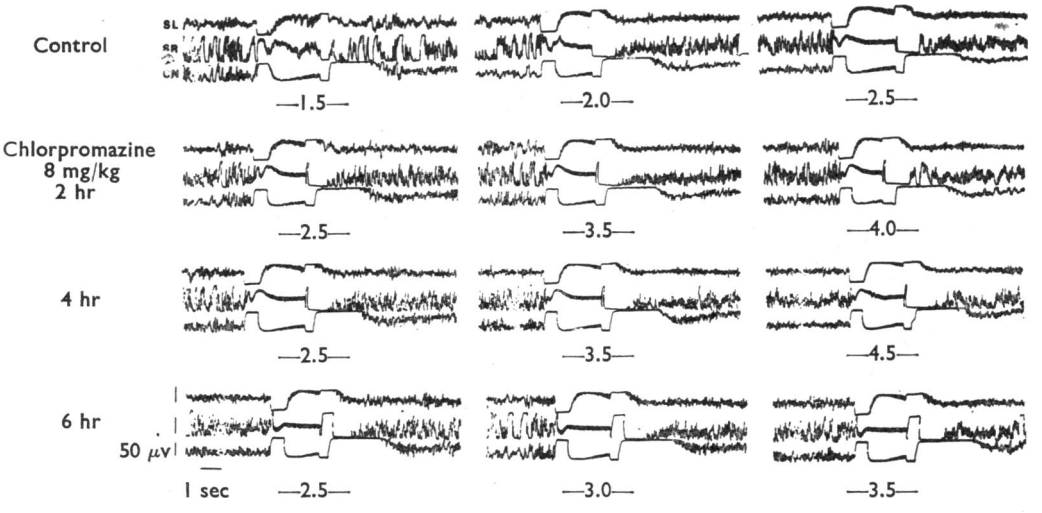

Fig. 4. The effect of chlorpromazine on the arousal thresholds in the cat. Electroencephalogram and behavioural arousal thresholds elicited by direct stimulation of the reticular formation before and after 8 mg/kg of chlorpromazine, intraperitoneally. Stimulation was during the periods indicated by horizontal bars, at the voltages shown. The last column shows behavioural arousal. Symbols are: SL, median suprasylvian cortex left; SR, medium suprasylvian cortex right; CN, caudate nucleus. Calibrations, 50 μV and 1 sec.

No effect on the recruiting response was observed after the four compounds in doses of 4.0 and 8.0 mg/kg. The Win compounds had little effect on the arousal response elicited from stimulation of the reticular formation in contrast to a small but consistent rise (1 to 2 V) in the arousal thresholds by chlorpromazine (Figs. 3 and 4). There was a slight tendency in most cats to be aroused somewhat more easily after the Win compounds as judged by more frequent incidents of spontaneous arousals and a slight decrease (0.5 V) in the arousal thresholds. However, these changes were not observed consistently.

DISCUSSION

Our results confirm the findings of Archer *et al.* (1962) that the three Win compounds potentiate hexobarbitone sleeping time in mice. Although quantitative differences between the Win compounds are not marked, they appear to be somewhat weaker than chlorpromazine in this test. As none of the drugs in the dosage range tested caused hypnosis *per se*, it is evident that these drugs prolong the duration of hexobarbitone hypnosis in a more than additive manner. Furthermore, the three Win compounds, like chlorpromazine, were able to re-induce sleep when injected intravenously into mice just recovered from hexobarbitone hypnosis. Of further interest is the observation that lactic acid itself significantly increased the duration of hexobarbitone hypnosis. The potentiating effect of glucose and many of its metabolites, including lactate, on barbiturate anaesthesia was first reported by Lamson, Greig & Robbins (1949) for guinea-pigs. Subsequent work (Lamson, Greig & Hobdy, 1951) demonstrated marked species differences to this response. The potentiating effect of lactic acid and other metabolites of glucose on barbiturate hypnosis is of considerable importance in the use of such substances as solvents.

In addition to a potentiating effect on barbiturate hypnosis, the Win compounds have been found to possess hypothermic activity and to afford protection against amphetamine toxicity in aggregated mice to a degree comparable with chlorpromazine. Subtle differences between the compounds were not evident in these tests. However, the three Win compounds were 1.5- to 3.0-times as toxic as chlorpromazine on intraperitoneal administration to mice. Although the Win compounds have been shown to exert adrenolytic activity (Archer *et al.*, 1962), the protection against amphetamine toxicity in grouped mice does not seem to be due to a direct antagonism of amphetamine *per se*, since little protection was offered by these drugs in isolated mice. Interestingly, tranquillizers like meprobamate and benactyzine are inactive in this test (Burn & Hobbs, 1958).

Of the three Win compounds, Win 18,501–2 alone appeared to be equipotent with chlorpromazine in blocking the conditioned avoidance response in rats, whereas Win 18,437 was three times weaker and Win 18,413–2 intermediate in activity. Our results with Win 18,501–2 on the conditioned avoidance response in rats agree with those reported by Edwards, Moon & Pearl (1962). Cole & Edwards (1964), however, found Win 18,437 to be virtually ineffective in blocking the avoidance response in rats when administered orally in doses up to 0.5 g/kg. The mode of administration of the drugs may account in part for the difference in response. Substitution of the indole nucleus by methoxy groups at positions 5 and 6 seems to exert a favourable influence on the sedative properties of these compounds. However, no generalizations can be made on the basis of the small number of compounds studied.

The variability in the responses of the cats to the effects of the Win compounds as well as chlorpromazine was rather striking in these studies and ranged from a complete lack of sleep in one animal to excessive sleep in another. The stressful effects of ataxia caused by these drugs may account in part for this difference in the response. However, it was not always possible to correlate restlessness and lack of sleep with ataxia. The difficulties involved in isolating specific drug effects on the central nervous system and behaviour from secondary manifestations due to toxic side-effects of the drugs, under these circumstances, are obvious.

No consistent changes in the spontaneous electrical activity of the brain in cats were observed after the Win compounds or chlorpromazine in doses up to 8 mg/kg. There was a tendency for low-voltage fast activity to predominate in the electroencephalogram of resting awake animals after the Win compounds. The results with chlorpromazine are consistent with the observations of most workers that the effects of pharmacological doses of chlorpromazine on the spontaneous electrical activity of the brain in the cat (Killam, Killam & Shaw, 1957), the rabbit (Gangloff & Monnier, 1957) and in man and the monkey (Monroe, Heath, Mickle & Miller, 1955) are relatively slight.

The Win compounds as well as chlorpromazine had little effect on the thalamic recruiting responses in doses up to 8 mg/kg. Previous reports on the effects of chlorpromazine on the recruiting responses are not in agreement. Killam & Killam (1956) observed that chlorpromazine in doses of 1 mg/kg slightly enhanced cortical recruitment, while doses of 2 to 8 mg/kg slightly depressed the recruiting responses in the unanaesthetized curarized cat. In the unanaesthetized rabbit, on the other hand, Gangloff & Monnier (1957) observed facilitation of the recruiting responses after 5 mg/kg of chlorpromazine. Differences in the preparations used and in the modes of administration of the drugs may account in part for our failure to observe any effect on the diffuse thalamic projection system.

Chlorpromazine in doses of 8 mg/kg consistently increased the electroencephalogram and behavioural arousal threshold by 1 to 2 V. These results are consistent with the observations of other workers regarding the effects of chlorpromazine on the reticular activating system in the cat (Killam *et al.*, 1957; Bradley & Key, 1958), the rabbit (Gangloff & Monnier, 1957) and the rat (Barraclough & Sawyer, 1957). In contrast to the effects of chlorpromazine, the three Win compounds did not raise the arousal threshold to stimulation of the reticular formation in doses up to 8 mg/kg. On the other hand, there was a slight tendency in most animals to be aroused somewhat more easily, as indicated by a greater incidence of spontaneous arousals and an occasional decrease in the arousal threshold. However, these changes were slight (0.5 V) and were not consistently observed.

The effects of the three Win compounds thus differ somewhat from those of chlorpromazine on the central nervous system of the cat. A consideration of these differences suggests that the effects of the Win compounds are more like reserpine, to which they bear some structural resemblance, than like chlorpromazine. It is to be noted that, in contrast to chlorpromazine, these drugs cause many effects, such as ptosis, lacrimation and salivation, which are reminiscent of the actions of reserpine. Yet there exist many differences between the Win compounds and reserpine. Prominent among these are the more rapid onset of action of the Win compounds and a lack of effect on brain 5-hydroxytryptamine (Archer *et al.*, 1962).

The slight stimulant effects of the Win compounds observed on the behaviour and electrical activity of the brain in cats does not seem to accord with the psycho-sedative properties of these compounds. A possible correlation might exist between these effects and the clinical observations of Durell & Pollin (1963) that in about one-third of the patients treated with 120 mg or more of Win 18,501–2 daily the drug induced a high degree of tension, restlessness and anxiety. In addition, Hollister, Overall, Kimbell, Bennet, Meyer & Caffey (1963) observed that Win 18,501–2 in daily doses of 165 mg was highly effective in " schizophrenic " and " depressive " patients but not in those classified as " paranoid."

These observations seem to indicate that the Win compounds exert mixed stimulant and depressant effects on the central nervous system. This is further supported by the observations made by Cole & Edwards (1964) that Win 18,501–2 in rather low doses (2 mg/kg, orally) potentiated the stimulant effect of dexamphetamine on motor activity in the rat, whereas larger doses depressed the dexamphetamine-induced hyperactivity.

These studies have brought out similarities as well as certain differences in the profile of central nervous activity between the Win compounds and chlorpromazine. Of the three Win compounds, Win 18,501–2, a methoxy-substituted indole, appears to be more potent and less toxic than the other two Win compounds.

SUMMARY

1. The psycho-sedative properties of three indolyl-ethyl-piperazine derivatives (Win 18,501–2, Win 18,437 and Win 18,413–2) were studied and compared with those of chlorpromazine.

2. The three Win compounds potentiated hexobarbitone sleeping time, caused hypothermia and afforded protection from amphetamine toxicity in aggregated mice to a degree comparable with chlorpromazine. However, all three compounds proved to be more toxic than chlorpromazine in acute toxicity studies.

3. Win 18,501–2 was equipotent with chlorpromazine in blocking conditioned avoidance response in rats, whereas Win 18,437 was three times weaker, and Win 18,413–2 had intermediate activity.

4. The Win compounds had little effect on the spontaneous electrical activity of the brain in cats and on the arousal responses elicited from stimulation of the reticular formation in contrast to a small but consistent rise in the arousal thresholds by chlorpromazine.

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