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BW 234U, (*cis*-9-[3-(3,5-dimethyl-1-piperazinyl)propyl]carbazole dihydrochloride): a novel antipsychotic agent

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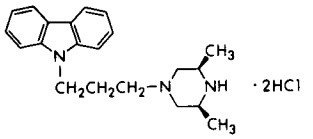
The capacity of neuroleptic drugs to antagonize the behavioural effects of the dopamine agonist, apomorphine, in animals has been used as a basis for identifying new compounds with potential antipsychotic actions in man (Fielding & Lal 1974). Experience has shown that neuroleptic drugs which are potent antagonists of apomorphine-induced stereotyped behaviour, produce a high incidence of extrapyramidal side effects and tardive dyskinesias in man (Niemegeers 1974; Berger et al 1978). In addition to stereotyped behaviour, however, apomorphine produces other behavioural effects. Thus, McKenzie (1971) reported that apomorphine elicited fighting in paired male rats and Costall et al (1979) reported that apomorphine elicited climbing behaviour in mice. Both of these behavioural effects can be antagonized by neuroleptic drugs. These considerations led to the formulation of a research program which had as its goal the development of a compound that would (1) block apomorphine-induced aggression in rats and apomorphine-induced climbing in mice, but (2) not block stereotyped behaviour in either species. From a theoretical point of view climbing and aggressiveness produced by apomorphine probably reflect stimulation of dopamine receptors in the limbic system whereas stereotyped behaviour reflects stimulation of dopamine receptors in the striatum (Fielding & Lal 1974; Costall et al 1979; Costall & Naylor 1981). Overactivity of the limbic system has been implicated in the etiology of psychotic behaviour in man (Hökfelt et al 1974). It was reasoned that a compound exhibiting selective blockade of climbing and aggressive behaviour would share with neuroleptic drugs the ability to influence cognitive and affective changes characteristic of psychosis, but unlike neuroleptic agents would not produce extrapyramidal side effects. The pharmacology of compound, BW 234U which evolved from this program, is presented below.



Central nervous system and behavioural pharmacology. BW 234U antagonized apomorphine-induced aggression (fighting behaviour as defined by McKenzie 1971) in rats by both the oral and i.p. routes (Fig. 1). By the oral route BW 234U had an ED50 value of 48 ± 6·9 mg kg^{-1}. The i.p. ED50 value for BW 234U was 12·5 ± 3·2 mg kg^{-1}. For comparison the i.p. ED50 for chlorpromazine was 5 ± 2·3 mg kg^{-1}. A dose of BW 234U equal to twice the ED50 for antagonizing apomorphine-induced aggression (25 mg kg^{-1} i.p.) had no effect on the stereotyped behaviour induced by 1, 5, or 15 mg kg^{-1} of apomorphine (Table 1). Doses of BW 234U of 50 mg kg^{-1} or higher also failed to block the stereotyped behaviour induced by apomorphine. However at these high doses some rats responded to the BW 234U and apomorphine combination with occasional myoclonic seizures. In contrast, a dose of chlorpromazine equal to two times its ED50 against apomorphine-induced aggression 10 mg kg^{-1} i.p., significantly reduced stereotyped behaviour evoked by apomorphine. BW 234U also blocked the climbing (ED50 value of 19 ± 4 mg kg^{-1} i.p.) but not the stereotyped behaviour induced by 2 mg kg^{-1}, s.c. apomorphine in mice. Climbing behaviour was elicited with apomorphine according to the technique of Costall et al (1979). Thus, BW 234U antagonized both apomorphine-induced aggression in rats and apomorphine-induced climbing behaviour in mice but differed from chlorpromazine in that it failed to block stereotyped behaviour.

Catalepsy, a behavioural effect of neuroleptic drugs in rodents, also correlates with a tendency to produce extrapyramidal side effects in man (Carlsson 1978). BW 234U did not produce catalepsy as judged by the technique of Morpurgo (1962) in rats at doses of 2 and 4 times its ED50 value for antagonizing apomorphine-induced aggression in rats (25 and 50 mg kg^{-1}, respectively). In contrast, chlorpromazine induced a dose-dependent catalepsy in rats which was observed at doses as low as 10 mg kg^{-1}, a dose

Table 1. Effects of BW 234U and chlorpromazine on apomorphine-induced stereotyped behaviour in rats.

Drug mg kg^{-1} i.p.	Mean scores ± s.e. after apomorphine: 1 mg kg^{-1}	5 mg kg^{-1}	15 mg kg^{-1}
Control	8·0 ± 0·6 (35)	15·8 ± 1·0 (30)	21·4 ± 1·8 (20)
BW 234U 25	8·1 ± 0·8 (4)	15·5 ± 3·1 (7)	20·2 ± 1·2 (7)
Chlorpromazine 10	0·5 ± 0·2* (6)	8·6 ± 2·3* (6)	16·1 ± 2·0** (10)

* $P < 0·01$ uing Student's t-test.
** $P < 0·05$.
( ) = number of animals.
Stereotyped behaviour was scored according to the procedure of Costall & Naylor (1973).

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approximately twice its ED50 value for antagonizing apomorphine-induced aggression. BW 234U also differed from chlorpromazine in that doses up to 4 times the ED50 value for antagonizing apomorphine-induced aggression failed to block shuttle box avoidance responding in rats. In contrast, chlorpromazine at its ED50 as an antagonist of apomorphine-induced aggression, 5 mg kg^{-1} i.p., blocked shuttle box avoidance in rats.

BW 234U was also an effective antagonist of aggressive behaviour in several other animals models. The ED50 for BW 234U as an inhibitor of muricidal (mouse-killing) behaviour in isolated male rats was 13 ± 4 mg kg^{-1} i.p. The ED50 value of BW 234U as an inhibitor of isolation-induced aggression in mice was 27·5 ± 3 mg kg^{-1} i.p.

Biochemical studies

Compounds which act as agonists or antagonists at dopamine receptor sites decrease and increase, respectively, the synthesis of [^{3}H]dopamine from [^{3}H]tyrosine (Nyback et al 1973: Carlsson 1978). Table 2 shows BW 234U at 50 mg kg^{-1} i.p. had no effect on the synthesis of [^{3}H]dopamine from [^{3}H]tyrosine while chlorpromazine, 20 mg kg^{-1} i.p. markedly increased synthesis of [^{3}H]dopamine. The dopamine agonist, apomorphine, at 5 mg kg^{-1}, inhibited dopamine synthesis.

In receptor binding studies (Table 3) chlorpromazine was found to be a good inhibitor of dopamine- and spiroperidol-binding to membrane fragments of rat striatum and olfactory tubercule. In contrast, BW 234U was a weak inhibitor of spiperone binding to striatal membrane fragments (IC50 5 × 10^{-5} M). At 10^{-4} M, the compound produced only 20–21% inhibition of dopamine and spiperone-binding to membrane fragments of rat olfactory tubercule and 26% inhibition of dopamine binding to membrane fragments of rat striatum.

The IC50 values for BW 234U as an inhibitor of dopamine-stimulated increases in cAMP in homogenates prepared from rat striatum was 1·0 × 10^{-4} M while the IC50 for chlorpromazine was 5·4 × 10^{-7} M. In homogenates of rat olfactory tubercule, BW 234U inhibited dopamine-stimulated increases in cAMP, having an IC50 of 1·8 × 10^{-4} M while chlorpromazine had an IC50 of 1·1 × 10^{-6} M. Thus BW 234U differs from chlorpromazine in that it has little or no effect on dopamine receptors.

Cardiovascular and autonomic studies

Intravenous boluses of 2·5 and 5·0 mg kg^{-1} of BW 234U in 3 anaesthetized, open-chested dogs produced transient, dose-dependent decreases in mean arterial pressure, heart rate and right ventricular contractile force of 10–20%. Ten mg kg^{-1} elicited changes of 40, 15 and 45%, in these parameters, respectively. Cardiac output increased ≈15–20% initially during the first 2 min following the injection and then decreased 5–15% below pretreatment levels. All three dogs survived the cumulative i.v. dose of 17·5 mg kg^{-1} administered within 30 min and were essentially back to control values within 30 min after the last intravenous injection. Thus, high intravenous doses of BW 234U produced only transient cardiovascular changes in these dogs. In closed-chested anaesthetized dogs, two consecutive intravenous doses of 5 mg kg^{-1} BW 234U has little or no effect on arterial blood pressure, heart rate and on PR, RR, QT intervals and QRS duration. Furthermore, BW 234U had no significant cardiovascular effects after oral doses of 5 and 10 mg kg^{-1} in a conscious dog.

Table 2. Effects of BW 234U, chlorpromazine and apomorphine on dopamine synthesis in the rat striatum.

Drug mg kg^{-1} i.p.	n	d min^{-1} g^{-1} – mean ± s.e. [^{3}H]DA	[^{3}H]AC	[^{3}H]T
Control	(26)	43 284 ± 1 446	4 044 ± 365	333 757 ± 24 688
Chlorpromazine 20	(10)	82 914 ± 8 920*	19 822 ± 1 610*	371 350 ± 27 201
Apomorphine 5	(3)	15 775 ± 3 645*	4 013 ± 978	342 967 ± 39 382
BW 234U 50	(4)	43 598 ± 1 193	4 117 ± 678	299 802 ± 10 473

* Denotes significance at the 0·01 level, using Student's *t*-test. [^{3}H]DA = tritiated dopamine, [^{3}H]AC = tritiated acidic catechols, [^{3}H]T = total tritium.
n = number of animals.

BW 234U at 1·0 mg kg^{-1} or at a cumulative dose of 3·5 mg kg^{-1} i.v. in 9 anaesthetized cats caused minimal and transient effects on blood pressure. There was no indication of dysfunction of the autonomic nervous system, suggesting that the compound did not block ganglionic or post-ganglionic receptors or grossly alter neurotransmitter release (noradrenaline or acetylcholine). Large cumulative doses of BW 234U (8·5 and 18·5 mg kg^{-1} i.v.) caused acute drops in blood pressure and heart rate during the 4 min infusion. The highest cumulative dose, 18·5 mg kg^{-1} i.v., often caused cardiovascular collapse and death. Concentrations of <10^{-5} M were without effect on guinea-pig atria, cat atria and papillary muscles and rabbit papillary muscle. Concentrations ≥10^{-5} M generally depressed rate and force

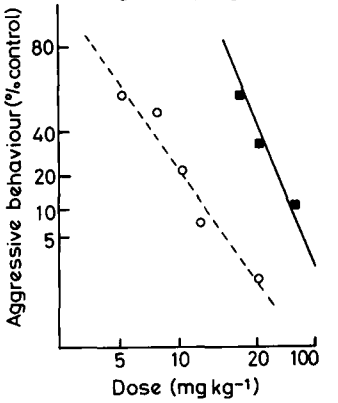

FIG. 1. Dose-response curves for the antagonism by BW 234U of apomorphine-induced aggression in the rat (McKenzie 1971). BW 234U i.p. ○; BW 234U p.o. ■. ED50 values calculated according to the method of Miller & Tainter (1944). A minimum of 20 animals were used to determine each point.

Table 3. Comparison of the potencies of chlorpromazine and BW 234U as inhibitors of the specific binding of [^{3}H]spiperone and [^{3}H]dopamine to membrane fragments of rat striatum and olfactory tubercule.

	Mean IC50 values			
	Striatum		Olfactory tubercule	
Drug	Dopamine	Spiperone	Dopamine	Spiperone
Chlor-promazine	5×10^{-6} M (3)	$3{\cdot}5 \times 10^{-7}$ M (3)	$6{\cdot}3 \times 10^{-6}$ M (3)	$6{\cdot}6 \times 10^{-6}$ M (3)
BW 234U	26*	5×10^{-5} M (3)	20* (3)	21* (3)

* Percent inhibition of specific binding of ligand at 10^{-4} M compound.
Binding studies were done according to the technique of Burt et al (1976) using [^{3}H]spiperone instead of [^{3}H]haloperidol as the ligand.
( ) = Number of individual experiments. Each point in each experiment was determined in duplicate.

of contractions of these tissues moderately and 10^{-4} M suppressed them markedly.

BW 234U at 10^{-5} M displaced the concentration-response curve to noradrenaline in rabbit aorta 2·1 fold to the right, had no effect on the responses of the aorta to angiotensin II, and displaced the concentration-response curves to isoprenaline and histamine in spontaneously beating guinea-pig atria 2·1 and 2·5 fold to the right. At 10^{-6} M, BW 234U did not shift significantly the cumulative concentration-response curves of the guinea-pig ileum to acetylcholine or histamine, but shifted (by 8× to the right) and depressed the maximum contraction of 5-HT. At 10^{-5} M, responses to all agonists were markedly depressed with a reduced maximum contraction. The data indicate that BW 234U lacks specific antihistaminic, anticholinergic or anti-5-HT effects.

Approximate acute LD50 values for BW 234U in rats were 80 mg kg^{-1} by the i.p. route and 907 mg kg^{-1} by the oral route. Approximate acute LD50 values in mice were 185 mg kg^{-1} by the i.p. route and 816 mg kg^{-1} by the oral route.

Discussion

Thus, BW 234U fulfils our criteria for a novel, potential antipsychotic compound since like neuroleptics it blocks the aggressive behaviour induced in rats and the climbing behaviour induced in mice by the dopamine agonist, apomorphine. However unlike neuroleptics it does not block stereotyped behaviour evoked by apomorphine. BW 234U, moreover, does not block dopamine receptors in either limbic or striatal structures nor affect measures of dopamine turnover, indicating that its antagonism of apomorphine-induced aggression and climbing behaviour are not directly mediated through dopamine receptors. BW 234U also blocks muricidal activity in rats and isolation-induced aggression in mice. Unlike neuroleptics, it has no effects on the conditioned avoidance response and is not cataleptogenic. Only negligible cardiovascular, anticholinergic, antihistaminergic, anti-5-HT and α- and β-adrenergic blocking effects are observed with BW 234U in isolated tissues at concentrations below 1×10^{-5} M. Current open trials being conducted with BW 234U in acute schizophrenic patients suggest that BW 234U has antipsychotic effects in man.

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