SHORT COMMUNICATION

BLOCKADE OF THE DOPAMINE DEPRESSOR RESPONSE BY MOLINDONE, A NEWLY INTRODUCED NEUROLEPTIC

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Summary: Pretreatment with the neuroleptics, haloperidol and molindone, significantly antagonized the dopamine-induced depressor response in the anaesthetized dogs. The depressor response to dopamine was however, not significantly affected by propranolol, atropine or antazoline pretreatment. The results suggest that molindone like haloperidol, is capable of blocking the vascular dopamine receptors responsible for mediating dopamine-induced vasodilatation in the coeliac, mesenteric and renal vascular beds and fall in blood pressure.

Key words: molindone dopamine depressor response dog

INTRODUCTION

Molindone hydrochloride, a dihydroindolone compound, is a recently introduced neuroleptic for the treatment of schizophrenia (1,2). Though chemically not related to other neuroleptics like the phenothiazines or the butyrophenones, it is capable of inducing catalepsy in rats and mice (11). As the cataleptogenic effect of neuroleptics has been attributed to blockade of striatal dopamine receptors (4,10) and further, as haloperidol has been reported to antagonize the hypotensive action of dopamine in anaesthetized dog (12), it was thought pertinent to study the effect of molindone on the depressor response to dopamine.

MATERIALS AND METHODS

Healthy mongrel dogs of either sex weighing between 7-10 *kg* were used. The animals were anaesthetized by the intravenous administration of 40 *mg/kg* of pentobarbitone sodium dissolved in normal saline. Anaesthesia was maintained with 5 *mg/kg* of intravenous injection of pentobarbitone sodium as needed. The blood pressure was recorded from the common carotid artery using a mercury manometer writing on a smoked kymograph. As the neuroleptics potentiate the CNS depressant effect of barbiturates (8), the dogs were maintained on artificial respiration throughout the experiment. Drugs were injected through the cannulated femoral vein.

Doses of dopamine were given in ascending order at 3 to 6 min intervals. After the sequence of dopamine doses, two responses to intravenous injection of a fixed dose of either isoprenaline, acetylcholine or histamine were elicited. After this sequence, either propranolol, atropine, antazoline, haloperidol or molindone was injected following dopamine. Haloperidol, propranolol and antazoline injection solutions were diluted with 10 *ml* of normal saline and infused intravenously over a period of 10 min to minimize the resultant fall in blood pressure, while atropine and molindone were administered in a bolus injection of 0.5 to 1 *ml*. Ten minutes after the end of the infusion or injection of atropine or molindone, the specific agonist (either isoprenaline, acetylcholine or histamine) and the sequence of dopamine doses were given as before. Isoprenaline, acetylcholine, histamine and dopamine were administered as a bolus injection in a volume ranging from 0.1 to 0.6 *ml* and were washed in with 2 *ml* of normal saline.

It should be noted that although the duration of each of the above experimental series with dopamine was long, no significant changes in the dopamine responses were noted during a similar interval in control dogs (n = 3) in which normal saline was infused in place of drug.

The following drugs were used: Dopamine hydrochloride (Merck), molindone hydrochloride (Moban', Endo Lab.), haloperidol (Serenace' injection, Searle) propranolol hydrochloride ('Ciplar' injection. Cipla) antazoline methane sulphonate ('Antistine' injection, Ciba), atropine sulphate, isoprenaline sulphate, histamine acid phosphate and acetylcholine chloride. The drugs were dissolved in or diluted with normal saline before injection. Ascorbic acid (0.2 *mg/ml*) was added as a preservative to the solutions of dopamine and isoprenaline. For each dose of the neuroleptic 5 dogs were used while for each dose of other pharmacological blockers 3 dogs were used.

For statistical analysis of the results a paired t" test was used.

RESULTS

Dopamine-induced pressure responses

The intravenous injections of small doses (1 to 8 $\mu g/kg$) of dopamine elicited purely depressor blood pressure response. The amine induced biphasic responses (i.e., an initial rise and a secondary fall of blood pressure in intermediate doses (16 to 32 $\mu g/kg$), and purely pressor response in large doses (64 to 128 $\mu g/kg$). As the pressor response induced by 32 $\mu g/kg$ dose of dopamine was more marked, and the depressor response was less as compared to the depressor response induced by 16 $\mu g/kg$ dose of dopamine, the effect of the pharmacological blocking agents was tested on the depressor responses induced by 1 to 16 $\mu g/kg$ of dopamine only.

Effect of non-neuroleptic blocking agents on dopamine-induced depressor responses

Propranolol (0.2 *mg/kg*), atropine (0.5 *mg/kg*) and antazoline (5 *mg/kg*), effectively blocked the depressor response to isoprenaline (2 *μg/kg*), acetylcholine (2 *μg/kg*) and histamine (2 *μg/kg*) respectively, but the depressor response to dopamine was not significantly ($P > 0.05$) affected by these blockers.

Effect of neuroleptics, haloperidol and molindone, on dopamine-induced depressor responses

Haloperidol (0.5, 1 and 2 *mg/kg*) and molindone (0.5, 1 and 2 *mg/kg*) pretreatment not only significatly ($P < 0.001$) reduced the depressor response to dopamine, but after haloperidol and molindone, the response to higher doses of dopamine was modified such that the depressor response was reduced and a pressor component appeared (Table I.). These neuroleptics produced transient depressor responses (10-20 mm Hg) *per se*.

TABLE I : Effect of haloperidol (HAL) and molindone (MOL) pretreatment on the depressor response induced by dopamine in anaesthetized dog.

Study	Treatment	*Mean fall in B.P. (mm Hg) ± S.E.M. induced by different doses of dopamine*				
		1 μg/kg	*2 μg/kg*	*4 μg/kg*	*8 μg/kg*	*16 μg/kg*
I.	1. Before HAL	14.0±1.41	23.2±3.03	32.4±2.78	36.8±2.41	38.8±2.43
	2. After HAL 0.5	5.2±1.35	10.8±1.62	16.4±1.71	20.0±1.82	21.6±2.35
		P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
II.	1. Before HAL	15.2±1.36	25.4±2.95	34.8±2.75	38.2±2.78	40.6±2.87
	2. After HAL 1.0	3.8±1.12	9.2±1.42	14.4±1.47	17.6±1.35	19.1±2.48
		P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
III.	1. Before HAL	14.8±1.38	24.2±2.75	32.8±2.24	37.3±2.62	40.4±2.78
	2. After HAL 2.0	0.0±0.00	5.4±1.28	10.2±1.44	13.5±1.82	15.2±2.37
			P<0.001	P<0.001	P<0.001	P<0.001
IV.	1. Before MOL	14.5±1.22	23.8±2.87	31.2±2.66	35.2±2.47	37.5±2.22
	2. After MOL 0.5	6.8±1.42	11.2±1.75	16.1±1.48	18.3±1.79	20.4±2.46
		P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
V.	1. Before MOL	15.5±1.28	26.2±2.74	35.6±2.98	38.8±2.54	41.3±3.15
	2. After MOL 1.0	4.2±1.15	11.5±1.27	15.2±1.36	18.2±1.48	21.7±2.27
		P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
VI.	1. Before MOL	16.2±1.52	27.4±2.67	35.4±2.45	40.0±2.25	42.5±3.45
	2. After MOL 2.0	0.0±0.00	7.2±1.28	12.5±1.17	15.2±1.26	17.2±2.95
			P<0.001	P<0.001	P<0.001	P<0.001

Numerals following HAL i.e. haloperidol and MOL i.e. molindone indicate their doses *(mg/kg)*.

DISCUSSION

Intravenous injections of small doses of dopamine elicit a purely depressor blo pressure response, while intermediate doses elicit a biphasic response i.e., an initial ri and a secondary fall of blood pressure, and large doses elicit a purely pressor response i dogs (6,9). The depressor effect of dopamine is primarily due to vasodilatation in th coeliac, mesenteric and renal vascular beds (5). As the depresso effect of dopamine not antagonised by atropine, beta-blockers, anthistamines or hexamethonium (6,9), bu is antagonized by haloperidol (12,13), a specific dopamine receptor blocking drug (7), it ha been suggested that the dopamine-induced vasodilatation in the coeliac, mesenteric an renal vascular beds occurs as a result of interaction of depamine with a specific dopamin receptor in these vascular beds. (14)

In our study the depressor response to dopamine was not blocked by atropine antazoline and propranolol. These findings are in agreement with those of Furukawa *et al* (6) and McDonald and Goldberg (9). However, the depressor effect was selectively antago nized by the neuroleptic agents, haloperidol and molindone. Our finding with haloperido is in agreement with that of Sampson *et al.* (12) and Van Rossum (13).

Molindone is reported to antagonize apomorphine-induced emesis in dogs and amphetamine stereotypy in rats (11). As apomorphine-induced emesis and amphetamine stereotypy are believed to be mediated through stimulation of central dopaminergic receptors (7), their antagonism by molindone suggests an interaction of molindone with central dopaminergic mechanisms. Further, the report of Bunney *et al.* (3) suggests that molindone exerts a central dopamine receptor blocking activity. Our present study shows that molindone is also capable of blocking the vascular dopamine receptors responsible for mediating dopamine-induced vasodilatation in the coeliac, mesenteric and renal vascular beds and fall in blood pressure.

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