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Studies on the Effects of Piperidine Derivatives on Blood Pressure and Smooth Muscles Contractions

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Ten substituted phenacyl derivatives of 4-hydroxypiperidine were synthesized and studied for their effects on the mean arterial blood pressure (MABP) in normotensive anaesthetized rats and smooth muscles contractions of isolated rabbit jejunum. Two derivatives caused fall in blood pressure at the dose of 10~20 mg/kg and one rise in blood pressure at the dose of 20 mg/kg. Two compounds exhibited biphasic response (hypotensive followed by hypertensive) and one gave triphasic response at 10 mg/kg dose. Rest of four derivatives were found devoid of any effect on mean arterial blood pressure up to the dose of 30 mg/kg. All the derivatives except two caused relaxant effect on the spontaneous contraction of rabbit jejunum at the dose range of 0.1~2 mg/kg.

Key words : Piperidine, Antihypertensive, Smooth muscle contraction

INTRODUCTION

Apart from analgesics, a wide range of therapeutic agents are available in which the piperidine nucleus is present. Specially hypotensive agents belonging to piperidine class of compounds are very important.

The continuing interest in the indole derivatives incorporating a tryptamine residue as potential antihypertensive agents stemmed from the work of Archibald *et al.* (1970), with 1,4-bis (indolylethyl) piperidine. In a similar attempt, Takai *et al.* (1985a), prepared a series of piperidine derivatives with various heterocyclic rings at the 4-position and tested for antihypertensive activity and other biological activities.

Several reports have appeared on antihypertensive piperidine derivatives with a heterocyclic ring in the spiro form (Maillard *et al.* 1970 and 1972 and Clark *et al.* 1983). Takai *et al.* (1985b), selected the spiropiperidine for further modification and resulting derivatives were evaluated for antihypertensive activity. Most of the compounds synthesized in this study showed strong hypotensive activities both in simultaneously hypertensive rats (SHR) and in normotensive rats. Moreover, among these, several compounds were found to produce a very large and long lasting decrease in blood pressure.

Very potent and competitive adrenergic antagonists, derived from (aryloxy) propanolamine blockers through introduction of a piperidine ring were introduced by Mauleon *et al.* (1988). This structural variation does not seem to markedly affect either potency or cardioselectivity, although one derivative was significantly more potent than propanalol.

In view of the therapeutic potential as well as the pharmacological significance of various piperidine derivatives noted in the foregoing review, it was considered to be of interest to synthesize (Saify *et al.* 1994b and Saeed *et al.* 1996 & 1997) substituted *N*-phenacyl derivatives of piperidine (Table I) through simple quaternization reaction. The resulting derivatives were evaluated for analgesic activity and a few selected derivatives among these were examined for their effects on brain monoamines levels in male albino mice (Saify *et al.* 1994b).

This paper includes screening these derivatives for their effects on mean arterial blood pressure (MABP) in normotensive anaesthetized rats and smooth muscles contractions.

MATERIALS AND METHODS

Effects on blood pressure

Wistar rats of either sex (200-250 gm) were used for the determination of effects of compounds on mean arterial blood pressure (MABP). The animals were anaesthetized with an intraperitoneal injection of thiopentone (pentothal, 70-90 mg/kg body weight). The right carotid artery was cannulated with heparinized

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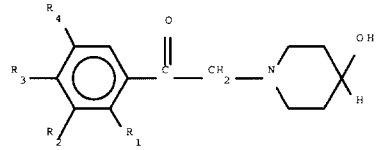
Table I. Substituted phenacyl derivatives of 4-Hydroxypiperidine and their physical data



Comp.	R1	R2	R3	R4	Colour/Shape	M.P.(°C)	Mol.Form.
II	H	H	CH_3	H	Brown Gummy Matter	-	$C_{14}H_{20}BrNO_2$
III	H	OCH_3	H	H	Yellow/Semisolid	-	$C_{14}H_{20}BrNO_3$
IV	H	H	OCH_3	H	Colourless/Cryst.	176-178	$C_{14}H_{20}BrNO_3$
V	OCH_3	H	OCH_3	H	Brown Solid	130-132	$C_{14}H_{20}BrNO_4$
VI	OCH_3	H	H	OCH_3	Colourless Semisolid	-	$C_{14}H_{20}BrNO_4$
VII	H	OH	OH	H	Ash White cryst.	148-150	$C_{13}H_{18}ClNO_4$
VIII	H	H	Ph	H	Colourless need.	212-215	$C_{19}H_{22}BrNO_2$
IX	H	H	Br	H	Colourless rods	216-218	$C_{13}H_{17}Br_2NO_2$
X	H	H	Cl	H	Light yellow Plates	238-240	$C_{13}H_{17}BrClNO_2$
XI	H	H	F	H	Colourless Powder	246-248	$C_{13}H_{17}ClFNO_2$

polyethylene tubing PE-50, which was connected to a pressure transducer coupled with a Grass 7D model Polygraph. The left jugular vein was cannulated with similar tubing to facilitate the I.V. injection of the test compounds. The rats were injected with heparin (1000 m/kg body weight) to prevent blood clotting.

After a 20 minutes period of equilibrium, the rats were injected I.V. with 0.2 ml saline (NaCl 0.9%) or with the same volume of test substance. Arterial blood pressure was allowed to return to the resting level between injections. Changes in blood pressure were recognized as the difference between the steady state values before and to the lowest readings after injection. Mean blood pressure was calculated as the diastolic blood pressure plus one third pulse width (Mcleod 1970).

Effects on smooth muscles contractions

New Zealand white rabbits (2-3 kg) of either sex starved for 24 hrs. were killed by cervical dislocation and exsanguinated. Segments of jejunum about 2 cm long were mounted in a 20 ml tissue bath containing Kreb's-Henseleit solution, maintained at 37°C and bubbled with a gas mixture of 95% O_2 and 5% CO_2. A preload of 1.0 g was applied and spontaneous contractions were recorded isotonically via a T-3 isotonic transducer on a Bioscience MD recorder. The tissues were allowed to equilibrate for 1 hr. before addition of any test compound (Gilani *et al.* 1994).

RESULTS

Effects on blood pressure

Table II presents the effects of 4-hydroxypiperidine (**I**) and its derivatives (**II-XI**) on mean arterial blood pressure (MABP) in normotensive anaesthetized rats.

i) Compound **I** is the starting material of all the derivatives and gave triphasic response at the dose of 30 mg/kg body weight.

ii) Compound **II** and **XI** showed hypotensive activity at the dose of 20 and 10 mg/kg respectively.

iii) Only one compound (**IV**) demonstrated hypertensive response at the dose of 20 mg/kg.

iv) Two compounds (**VIII** and **IX**) exhibited biphasic response (hypotensive followed by hypertensive) at the dose of 10 mg/kg.

v) Like starting material, compound **X** also gave triphasic response but at lower dose, i.e. 10 mg/kg.

vi) Rest of the compounds (**III, V- VII**) were devoid

Table II. Effects of 4-hydroxypiperidine.HCl (**I**) and its derivatives (**II-XI**) on mean arterial blood pressure (MABP) in normotensive anaesthetized rats

S.No	Compound	Dose (mg/ml)	Response	% Change in B.P. (mm Hg)
1	**I**	30.0	Triphasic	-
2	**II**	20.0	Hypotensive	- 46.3
3	**III**	30.0	Inactive	-
4	**IV**	20.0	Hypertensive	+ 39.8
5	**V**	30.0	Inactive	-
6	**VI**	30.0	Inactive	-
7	**VII**	30.0	Inactive	-
8	**VIII**	10.0	Biphasic	- 62.0, + 22.0
9	**IX**	10.0	Biphasic	- 40.0, + 24.0
10	**X**	10.0	Triphasic	-
11	**XI**	10.0	Hypotensive	- 82.2

of any effect on mean arterial blood pressure upto the dose of 30 mg/kg.

Effects on smooth muscles contractions

Substituted phenacyl derivatives of 4-hydroxypiperidine were also studied for their effects on the spontaneous contractions of isolated rabbit jejunum and results are presented in Table III. All the derivatives except two (**VI** and **VII**) caused relaxant effect on smooth muscle contractions at the dose range of 0.1-1 mg/ml whereas these two were found inactive upto the dose of 2 mg/ml.

Among the eight active compounds, one (**VIII**) showed relaxant effect at the dose of 0.1 mg/ml, five (**II-IV** and **X, XI**) at 0.3 mg/ml and one each (**V** and **IX**) at 1 mg/ml and 2 mg/ml dose respectively.

DISCUSSION

Compound **I** being the starting material of 4-hydroxypiperidine series, exhibited triphasic response at the dose of 30 mg/kg. Only two compounds (**II** and **XI**) showed hypotensive response among all the derivatives. Compound **II** having a *para* methyl substituted phenacyl moiety as a part of it's molecule, showed 46.3% fall in blood pressure at 20 mg/kg dose whereas compound **XI** being a *para*-fluoro substituted derivative, displayed hypotensive response at a smaller dose (10 mg/kg) with profound reduction in blood pressure (82.2%). Among the four methoxy derivatives, only *para* methoxy derivative (**IV**) showed hypertensive response (39.8% change in blood pressure) at the dose of 20 mg/kg. Rest of methoxy derivatives as well as compound **VII**, dihydroxy substituted derivative were altogether devoid of any effect on blood pressure upto the dose of 30 mg/kg.

Compound **VIII** and **IX**, former being *para* phenyl and latter, *para* bromo substituted derivative exhibited biphasic response (hypotensive followed by hypertensive) at the dose of 10 mg/kg. Like starting material, *para* chloro substituted derivative (**X**) also showed triphasic response but at a lower dose i.e. 10 mg/kg.

Table III. Effect of piperidine derivatives (**II-XI**) on spontaneous contractions of isolated rabbit jejunum.

S.No	Compound	Dose (mg/ml)	Response
1	II	0.3	Relaxant
2	III	0.3	Relaxant
3	IV	0.3	Relaxant
4	V	1.0	Relaxant
5	VI	2.0	Inactive
6	VII	2.0	Inactive
7	VIII	0.1	Relaxant
8	IX	2.0	Relaxant
9	X	0.3	Relaxant
10	XI	0.3	Relaxant

In the *in vivo* and *in vitro* studies, the compounds **IV** was found hypertensive as well as spasmolytic (smooth muscle relaxant), while other (**II** and **XI**) showed hypotensive along-with spasmolytic activity.

It is not unreasonable that norepinephrine (NE) is hypertensive in the anaesthetized rats but exhibits spasmolytic activity in non-vascular smooth muscles (Weiner 1985). Though the compounds understudy were not tested for the detailed mechanism of action but it can be speculated that this pattern of activity (hypertensive and spasmolytic) may be similar to that of norepinephrine.

However, for the compounds which exhibited spasmolytic activity in non-vascular smooth muscle (jejunum) and also lowered blood pressure, different explanation is required. The calcium channel blocking drugs are well known for their hypotensive action as well as spasmolytic activity, because this class of drugs relaxes both vascular and non-vascular smooth muscles as calcium is involved in all types of smooth muscle contractions (Brading 1981 and Bolton 1979). Therefore, the hypotensive alongwith spasmolytic activity observed with some of the test compounds may be explained similar to that of calcium channel blocking activity, though direct evidence is lacking and further studies are needed to confirm this.

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