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# A STUDY ON THE EFFECTS OF SOME NEW DERIVATIVES OF PIPERIDINE ON NEUROTRANSMITTERS

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**ABSTRACT**

Four chemically synthesized derivatives of piperidine were subjected to evaluate their pharmacological actions on Nervous System in male albino mice. The effects on neurotransmitters such as catechol amine and indolamine assuming that these derivatives might alter them differently, studied by HPLC-EC method. The result revealed that brain dopamine and catecholaminc were altered by most of these derivatives at the doses of 100mg/kg body weight.

## INTRODUCTION

The concept of chemical neurotransmitters arose from the classical experiment of Otto Loewi, who was first to demonstrate that the transmissions of nerve impulse are accompanied by chemical substances. The process is termed as neurochemical transmission and the chemicals released have been called neurotransmitters (Zygmunt et. al. 1987). The central nervous system (CNS) has excitatory and some inhibitory transmitters stored in different nerve cells. These are probably Acetylcholine, Dopamine, Noradernaline, 5TH. Gamma aminobutyric acid, certain amino acids and substance P. The drugs affecting the nervous system mostly act on these specialized nerve cells of the grey matter and produce either stimulation or depression (Ghosh 1982). As evident from the literature, the substituted piperidine derivatives exhibited potential therapeutic properties in addition to having pharmacological activities (Millard et al.. 1970, Archibald et al.. 1971 and Iorio & Klee, 1977), many researchers attached towards the synthesis and biological evaluation of the substituted N-Phenacyl piperidinium carboxamide derivatives (Goldsmith et al., 1952 and Reynold, 1979).

In a similar attempt, Takai et al. (1985), prepared a series of piperidine derivatives and tested for antihypertensive and other biological activities. Attempts were made to find new neuroleptics and found that the piperidine derivatives have high affinity for CNS (Scriabine et al., 1980 and Obase et al., 1982).

Considerable progress has been made in identifying these chemical transmitters, in large part because of the microclectrode technique and immunoassay, immuno-histochemical staining and radio chemical techniques as well as electron microscope, spectrophotometry and high performance liquid chromatography (HPLC) techniques (Poye, 1995). In order to investigate the possible role of these piperidine derivatives in the release of neurochemical transmitters, the present study has been carried out by using I IPLC technique.

## MATERIALS AND METHOD

***Drugs and Chemicals:***

Synthetic derivatives of piperidine indicated as (II), (IV), (VII) and (IX) are used as drugs (complete names given on further pages). Reagents used were of analytical grade. The purity and identity of all the reagents and synthesized compounds were confirmed by .UV, IR, Mass and NMR studies. Pethidine and saline were used as standard and control respectively.

***Animals:***

Male Albino mice (locally bred) were obtained from HU Research Institute of Chemistry, University of Karachi. Their weights were ranged from 25-30g. and caged individually in the same environmental conditions for about four days before experimentation.

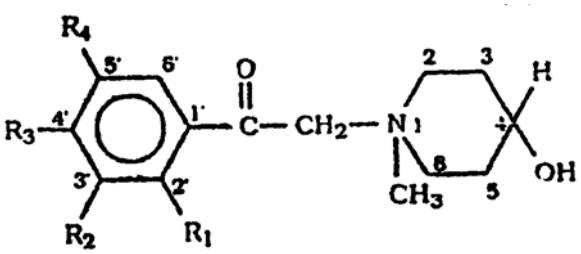
***Extraction and Estimation Procedure:***

The synthetic compounds were dissolved in the water for injection and injected to the test animals intraperitoneally (i.p) at the doses of 100mg/kg body weight. Pethidine and saline were also injected i.p to the standard and control respectively. Animals were killed I hours after the saline or lest compounds injection. Brains taken out within one minute, dipped into ice-cold saline and were stored at -70°C. Extraction medium was prepared by mixing 3m1. Perchloricacid, 0.1g. Sodium metabisulphite, 0.001g. ethylenediamine tetra acetic acid (EDTA) and 0.01g. cystein and volume was made upto 100m1. (Haleem el al., 1990). Brain samples were homogenized in 5 volumes of extraction medium and centrifuged. The clear supernatant was decanted into appenderoftubes for storage until analysis. 5-hydroxytryptamine (5HT), 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA), Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined by HPLC-EC method at 0.8v electrode potential. A 5U shrimp-pack CLC ODS, 4.6mm ID 15cm separation column was used. The solvent system is methanol (18%), Octylsodium sulphate buffer (PH 2.9). Samples from saline, pethidine and test compounds injected animals were run in a balanced design using 20 micro loop injector.

***Statistical Analysis:***

Data were analyzed by one way ANOVA. Post hoc comparison were done by New-

man Keuls test. Difference were considered significant when P<0.0.




(II) R I=R2=R4=H, R3-Br, X=Br.
1 Methyl-l (4-bromo) phenacyl-4-hydroxy piperidinium bromide.
(IV) R1=R3=R4=H, R2=$OCH_3$X=Br.
1-Methyl-1 (3'-methoxy) phenacyl-4-hdroxy piperidinium bromide
(VII) R1-R2=R4=H, R3=CI, X=Br,
1-Methyl-1 (4'-chloro) phenacyl-4-hdroxy piperidinium bromide
(IX) R1=R2=R4=H, R3=CH3, X=Br.
I-Methyl-l (4'-Methyl) phenacyl-4-hdroxy piperidinum bromide

## RESULTS AND DISCUSSIONS

Taking this fact into consideration that clinically employed phenacyl piperidine analgesics might induce neurotoxic actions on dopamine neurons in the brain (Ross J.B. et al., 1986), it is proposed to investigate the effects of these newly synthesized N-Phenacyl derivatives of piperidine on brain catecholamine and indolamine metabolism in mice (I00 mg/kg body weight) assuming that these derivatives might alter them differently.

The results of this study are presented in the table with representative figures.

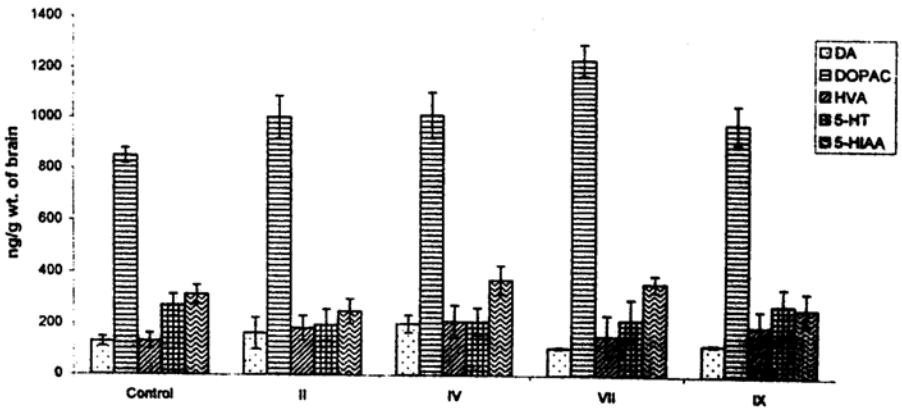


Fig. 1: Effect of N-methyle piperidine derivative (II, IV, VII and IX) on catecholamine and indolamine levels (ng/g) in mice brain I hour after the injection.

**Table-1**

Effect of N-methyl piperidine derivatives (II, IV, VII and IX) on catechacholamine & indolamine levels (ng/g) in mice brain 1 hours after the injection. Values are mean ± S.D. (n=5). Difference significant by Newmann-keuls test were p <0.01 from control following one way ANOVA.

| Neurotransmitters/ Metabolites | Control Water for injection | II | IV | VII | IX | ANOVA DIFF.4,25 F | P |
|---|---|---|---|---|---|---|---|
| DA | 130±18 | 164±62 | 203±34 | 110±04 | 124±04 | 0.98 | P≤ 0.01 |
| DOPAC | 849±30 | 1005±84 | 1017±91 | 1240±62 | 986±76 | 0.67 | P≤ 0.01 |
| HVA | 133±30 | 186±48 | 214±64 | 157±83 | 199±64 | 1.37 | P≤ 0.01 |
| 5HT | 272±43 | 199±61 | 214±54 | 222±80 | 284±66 | 1.4 | P≤ 0.01 |
| 5HIAA | 314±36 | 252±48 | 376±55 | 364±32 | 269±66 | 0.59 | P≤ 0.01 |

From the table and figs. It is evident that the administration of most of the derivatives increased brain dopamine (DA) levels with respect to control. Only compounds VII and IX cause a decrease in DA levels and it is also evident from the fig. that the injection of these compounds (IV & IX) enhance the levels of DOPAC and HVA. The enhancement of both DA and its metabolites DOPAC and HVA following the administration of most of the derivatives in the series are observed in the present study suggest an increase turnover of D.A.

An increase in the activity of particularly, rate limiting catecholamine synthesizing enzyme tyrosine hydroxlase (Sved, A.F. and Fernstrom. J.R, 1981) can explain the findings.

An acute deficiency to DA produced by 4'-chloro (VII) and 4'- methyl (IX) derivatives led to the conclusion that these may have neurotoxic effect particularly on dopaminergic neurons. However, an increase in DOPAC concentration by compounds VII and IX associated with increase in HVA by the same compounds suggest that the observed decrease in DA level following the administration of compound IX may have occurred because of an acute increase in the release of monoamines.

The fig. also shows that the metabolism of 5HT increases significantly followed by the administration of compounds (IV, VII & IX).

It is evident from the fig. that levels of 5HIAA increase by the effect of these newly synthesized derivatives. A role of indolamine in the antinociceptive effects of morphine

is often described in animal studies (Samanin et al., 1987). The present study shows that ad-ministration of piperidine derivatives increases brain serotonin metabolism. This may occur because of an increase in the availability of tryptophan to the brain or due to an in-crease in the activity of tryptophan hydroxylase (Schaechter, JD. et al., 1990).

## CONCLUSION

The present study reveals that these newly synthesized derivatives *of* piperidine II, IV, VII & IX) have shown considerable effects on the enhancement of both serotonin and catecholamine metabolism. They must he used in psychotic conditions carefully.

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