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PHARMACOLOGICAL EVALUATION OF NEWLY SYNTHESIZED PIPERIDINIUM DERIVATIVES FOR THEIR ANALGESIC ACTIVITY

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ABSTRACT

Two chemically synthesized piperidinium derivatives i.e. 1-melhyl-1-(3,4) dihydroxy phenacyl-4-hydroxy piperidinium chloride and 1-methyl-(4-p) methoxy phenacyl 4-hydroxy pipridinium bromide have been valuated for their analgesic activity in intact albino mice by tail immersion method because of their structural similarity with opioids. Both the compounds were administered in the doses of 50 mg/kg the were compared with pethidine used as reference drug. The control animal received only the vehicle. The present study suggested that the both compounds exhibit significant analgesic activity.

INTRODUCTION

Management of pain is essential to good medical practice and required careful consideration of proper dose, type of drug and the disease being treated. Pain may be treated non-specifically with drugs, physical measures, nerve block, surgery and by other measures. Generally the analgesic drugs used in therapeutics are either narcotic e.g. opioid or non-narcotic e.g. salicylates. The opium preparations provide a relief of severe pain of different origins. They exert their central analgesic effects through the opioid receptors currently our more detailed information is confined to knowledge concerning the mu, kappa and delta receptors (Paterson et al., 1981; Zukin and Zukin 1984). They are used for the management of constant and severe pain. Since daily administration of opioids produce tolerance which is closely associated to addiction that causes both physical and psychical dependence on the drug (Report, 1960). To avoid these undesirable effects it is necessary to synthesize more and mom new compounds and their derivatives, that may produce maximum therapeutic effects with fewer side effects against various types of pain. Piperidinium derivatives also exhibit analgesic activity, therefore in present investigation it was suggested that the structural modification of piperidinium molecule might be successful ill developing the desired analgesic drugs.

MATERIALS AND METHODS

Dugs and Chemicals:

Both the piperidinium derivatives 1-methyl-l-(3, 4) dihydroxy phenacyl-4-hydroxy piperidinium chloride and 1-methyl-1(4-chloro)phenacvl-4-hydroxy piperidinium

bromide were synthesized in Dr. Z.S. Saifv Laboratory, Faculty of Pharmacy, University of Karachi.

The reagents used in the synthesis were of analytical grade. The purity and identity of these compounds was confirmed by UV, NMR and MS studies. Pethidine NCl and gum tragacanth, were used as standard drug and vehicle respectively.

Animals:

Intact albino mice of either sex obtained from HET Research Institute of Chemistry, University of Karachi, were used in (his study. The weight of all the mice ranged from 25-30 g. All the mice were divided in the groups of five each. They were maintained at a temperature of 30 ± 1°C. and kept on proper diet and water before the administration of drugs.

Method of assessment *of* analgesia:

In present study the analgesia was assessed by employing tail immersion method (Distasi et al., 1988). The mice were held in a suitable restrained with the whole tail extending out. The distal end of the tail (2-3 cm) was immersed in the water bath thermostatically maintained at 51°C. The reaction time (in seconds) to withdraw the tail from hot water was recorded initially as tail flick latency before the administration of any drug (as pre-drug tail flick Itency) and then recorded at the time interval of 30, 60, 90, 120, 150, 180 and 120 minutes after the administration of the test dung (post drug tail flick latency) and the standard drug. The maximum immersion time of 30 seconds was maintained to avoid the thermal injury of the tail. All the drugs were administered orally by intubation in the doses of 50 mg/kg as a suspension in 1% gum tragacanth. The control animals received the vehicle only.

The criterion of analgesia was post-drag latency which was greats than two times the pre-drug avenge latency (Janssen et al., 1963). Tail flick latency difference or mean increase in latency after drug administration was used to indicate the analgesia produced by test and standard drugs. Analgesia TFLD was calculated as follows.

Analgesia TFLD = Post drag tail flick latency - Pre drug tail flick latency

Statistical analysis:

Values for analgesic activity were expressed as “mean increase in latency after drug administration ± SEM” in terms of seconds. The significance of difference between means was determined by student's t-lest. Values of $P < 0.05$ were considered significant and $P < 0.01$ as highly significant. All statistical procedures were performed according to the method of Alcaraz and Jimenez (1989).

RESULTS

The analgesic effects of gum tragacanth (Vehicle). pethidine, 1-methyl-l-(3-4) dihydroxy phenacvl-4-hydroxy piperidinium chloride and 1-methyl-(4p) methoxy phenacyl 4-hydroxy piperidinium bromide recorded, are summarized in Table-1.

The piperidinium derivatives tested in the study showed significant analgesic activity, sometimes even greater than the standard analgesic drug pethidine. The piperidinium derivatives 1-methyl-l-(3, 4) dihydroxy phenacyl-4-hydroxy piperidinium chloride produced an equipotent analgesic response as compared to pethidine after 30 minutes of drug administration, however a highly significant increase in the analgesic response of the piperidinium chloride was observed after 60, 90 and 120 minutes.

The another pipridinium derivative 1-methyl-(4p) methoxv phenacyl 4-hvdroxy piperidinium bromide showed highly significant analgesic activity after 30, 60, 120 and 150 minutes of drug administration, a more effective analgesic response in comparison to pethidine.

DISCUSSION

Since narcotic analgesic drugs possess such diverse molecular structures, it may at first glance appear difficult to conceive of any molecular basis for the analgesic action of these compounds. Closer examination, however, reveals several common structural requirements for analgesic activity. Although the phenanthrene nucleus of morphine can be modified or even eliminated, the piperidine ring is essential. The nitrogen atom this ring is also necessary. The oxygen atom of the phenolic hydroxyl group attached to the piperidine ring likewise cannot be eliminated without loss of activity.

The piperidinium derivatives tested in present study revealed highly significant analgesic activity which might be due to the presence of piperidine ring in the chemical structure. The duration of action of the piperidinium derivatives was also found to be longer than pethidine which may be either due to slow rate of metabolism or decreased rate of elimination of the drugs from the body. These derivatives also do not revealed any gross toxic effects or behavioural changes. No mortality was observed p to a period of about 30 days.

CONCLUSION

Present study reveals piperidinium derivatives to be relatively safe and potent analgesic drugs, however further investigations have to be carried out on larger animal groups to establish the precise mechanism of action, acute and chronic toxicity and pharrnacokinetic pattern of the derivatives.

Table-1
Analgesic Effects of Piperidinium Derivatives in Mouse Tail Immersion Method

Treatment	Dose/kg orally	Anlgesia TFLD or mean increase in latency after administration ± S.E.M. (s) ± 30	± 60	± 90	± 120	± 150	± 180	± 210
Gum tragacanth 1%	50 mg	0.28 ± 0.13	0.60 ± 0.16	0.80 ± 0.22	0.68 ± 0.21	0.72 ± 0.23	0.88 ± 0.10	0.52 ± 0.17
Pathidine	50 mg	1.28 ± 0.39*	1.56 ± 0.34*	1.56 ± 0.28*	1.72 ± 0.23**	1.52 ± 0.23**	1.40 ± 0.29	1.36 ± 0.48
1-methyl-1-(3, 4) dihydroxy phenacyl-4-hydroxy piperidinium chloride	50 mg	0.92 ± 0.04*	1.52 ± 0.12**	2.04 ± 0.23**	2.32 ± 0.57**	1.52 ± 0.27*	1.04 ± 0.19	0.84 ± 0.13*
1-Methyl-(4p) methoxy phenacyl 4-hydroxy piperidinium bromide	50	2.08 ± 0.20**	2.48 ± 0.38**	2.72 ± 0.24**	2.44 ± 0.09**	1.76 ± 0.22**	1.72 ± 0.39*	1.40 ± 0.30*

n/group = 5
*P < 0.05
**P < 0.01

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