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Research Article

THE STRUCTURAL MODIFICATION CAUSES THE ENHANCEMENT OF ANALGESIC ACTIVITY OF 4-(4′ CHLORO –PHENYL)-4- HYDROXY PIPERIDINE

KIRAN RAFIQ*[1], ZAFAR SAIED SAIFY[2], RANA KAUSAR[3], NAJIA RAHIM[4], SABAHAT NAEEM[4]

[1]Faculty of Pharmacy, Jinnah Sind Medical University, Karachi, Pakistan, [2]H. E. J., Karachi University. Pakistan, [3] Federal Urdu University (FUUAST), Karachi, Pakistan, [4]Dow College of Pharmacy, Dow University of Health Sciences. Email: kiranrafiq@hotmail.com

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ABSTRACT

Objective- The outstanding position of piperidine analogues has proven them an important core in the structures of pharmaceutically active molecules, naturally occurring alkaloids, pharmaceuticals and as synthetic intermediates with interesting biological, physical and pharmacological behaviors. The piperidine ring containing compound like pethidine having strong opiod analgesic activity, more potent than codein and controls the pain of smooth muscle spasm. Because of having similarity in structure the present study was aimed to estimate the analgesic activity of synthesized derivatives of 4-(4′-Chlorophenyl)-4-hydroxy piperidine.

Method- The present study was conducted in animal model, mice by using Pethidine as standard drug. For which the Eddy's hot plate method was adopted and analgesia (mean increase in latency) was observed.

Result- The result showed the more prominent response of substituted compound than the parent one "4-(4′-Chlorophenyl)-4-hydroxy piperidine" and it was studied that alteration in the molecule structure is accountable for a better analgesic response.

Conclusion- The studies proved the positive pharmacological responsiveness of the combination of 4-(4′-Chlorophenyl)-4-hydroxy piperidine with phencyl halides. These synthesized derivatives will establish as potent analgesics.

Keywords: Alkaloids, Opiod, Analgesic, Piperidine.

INTRODUCTION

The analgesic activity engages a multifarious communication of nervous system from the skin and the muscule tissues to the brain. The opioid receptors are responsible for producing nociception and also causes antinociception effects. It is closely connected with all CNS areas. Hence the facts reveal that the analgesia and antinoceception are closely and strongly associated with binding of opiod receptor with a suitable psychoactive chemical, an opiate [1, 2]. The credit that opioid therapy can reduce pain and improve functioning in many patients with chronic pain has directed drug experts to recommend opioids [3]. The piperidine ring containing compounds due to having similarity in the structure with morphine belongs to the same class of drug and cause analgesia by blocking the signaling pathways against pain as like Pethidine (Figure-1), Bemidone and Ketobemidone that are more effective analgesic compounds [4] because the substituted piperidine molecule exhibited potential therapeutic properties due to the structure activity relationship and good receptor binding and considered as leading nucleus used for the treatment pain and inflammation [5, 6]. There is a long series of piperidine derivatives which has proved potent antinociceptive agent. Among them Fentanyl (Figure-2), a synthetic opiod analgesic, was derivatized from 1-Phenethyl-4-piperidone, exhibited a better profile of activity as compare to morphine [7]. The substitution was studied on two different positions of piperidine ring. The structural activity relationship revealed that substitution on position 3 by the group larger than methyl reduces the analgesic potency due to involved steric factor [8].

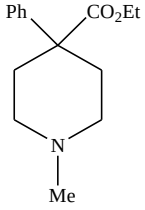

Figure-1: Pethidine

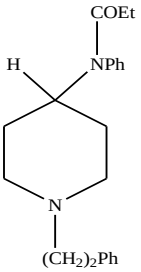

Figure-2: Fentanyl

Ohmefentanyl and Remifentanyl are extremely potent analgesic agents with highest receptor affinity and selectivity for the opioid μ receptors [9, 10].

METHOD

The analgesic activity of synthesized derivatives of 4-(4′-Chlorophenyl)-4-hydroxy piperidine was conducted by Eddy's hot plate method [11, 12]. These compounds were synthesized by reacting with different phenacyl halide according to the designed reaction scheme [13] For conducting the analgesic study albino mice of either sex. The weight of all the mice ranged from 20-30g that were divided in the groups of six each. The animals were provided standard colony conditions (12 hrs night and 12hrs dark) as proper diet and water before the administration of drugs and were kept at a temperature of 30 ± 1°C. The parent compound 4-4-Chlorophenyl Piperidine and derivatives were tested orally for analgesic effect at the effective dose of 50mg/ Kg weight (as 25mg/ Kg weight was found ineffective and 75mg/ Kg weight was observed lethal. Pethidine (5mg/Kg) and gum tragacanth were used as standard drug and vehicle respectively. The activity of compounds was assessed at a temperature of 55±1°C. The control groups received only the vehicle. Analgesic effects were observed at 30, 60, 90, 120, and180 minutes after administration and six animals were taken in a group. The analgesia was measured by the writhings after

the administration of drugs (compounds) and the results were summarized in the form of analgesic activity (Tables: 1) that was expressed as analgesia, mean increase in latency after drug administration ± SEM and was calculated. Student's t-test was applied for statistical analysis and P<0.05 or P<0.01 were considered as significant or highly significant values respectively.

RESULTS AND DISCUSSIONS

Piperidine ring containing compounds are identified as potent analgesic. Consequently extensive research has been done for the substitution of piperidine to get better moiety for the management of pain. Structural modification can lead to achieve good quality analgesics having little side effects with potent pain controlling ability [14, 15]. Number of other piperidine derivatives having significant analgesic activity were synthesized by different workers and among them mostly substituted piperidine derivatives were experimentally proved strong antinociceptive agent [16]. During the present study the synthsized molecules were analysed for the analgesic behaviour (Table-1) by producing thermal pain stimuli [17] and it was observed that the parent compound 4-(4′-Chlorophenyl)-4-hydroxy piperdine showed negligible analgesic effect and hence it was considered as inactive and non significant analgesic. But Interestingly encouraging results were obtained by all the phenacyl derivatives of 4-(4′-Chlorophenyl)-4-Hydroxy piperdine proved active analgesic. As 1-(1′′-Adamantan acyl)-4-(4′-chlorophenyl)-4-hydroxy piperidinium Hydrobromide (I), showed analgesic response highly significant level (p<0.01) after 30 minutes that remained till one hour and observed significant (p<0, 05) after 90 and 120 minutes but response was shown inactive after 180 minutes. Derivative 1-(6′′-Methyluracil)-4-(4′-chlorophenyl)-4-hydroxy piperidinium Hydrochloride (III) also proved an excellent analgesic by giving the response of highly significant level with more a quick onset immediately after 30 minutes that was observed highly significant till 180minutes. Derivative, 1-(1′′-Phenoxypropyl)-4-(4′-chlorophenyl)-4-hydroxy piperidinim Hydrobromide (IV), exhibited strong analgesia of significant level (p<0.05) immediately after 30 minutes that was observed constant till two hours and after that the response become of highly significant level. Derivative, 1-(3′′-Phenylpropyl)-4-(4′-chlorophenyl)-4-hydroxy piperidinium hydrobromide (V), exhibited potent analgesic response of highly significant level (p<0.01) after one hour of drug administration that was observed constant till 180 minutes. The substitution of methyl group at the phenacyl nitrogen was responsible for a significant change in the antinoceceptive activity of piperidine. All the synthesized derivatives were belonging to opioid analgesics group. These investigations were conducted to study the structure-activity-relationship (SAR) of the subsituent group on the nitrogen of piperidine derivatives. The results showed that the methyl group severely enhanced the analgesic potency. Whereas the duration of action usually did not depend on the methyl group substitution, prolonged action of the derivatives might due to the substitution of group in structure such as methoxy that may modify the duration of action by affecting the pharmacokinetic properties. SAR studies with refrence to analgesia suggested that the opiod receptors were responsible for antinociceptive, hence in the series of substituted piperidine analogues, the nature of receptor binding with the structure of whole molecule describes analgesic response and hence the strength and also the duration of action may be influenced only by the steric effect. In present study though all the synthesized piperidine were encouraging, whenevaluated for analgesia. Compounds having significant and highly significan results, can be selected for further studies regarding antinoceciptive activity.

Table-1: Analgesic Effects of 4-(4′-Chlorophenyl)-4-Hydroxy Piperdine Derivatives

Dose(Oral) 50mg/Kg	Analgesia (mean increase in latency after drug administration ± SEM)				
Time	30min	60min	90min	120min	180min
Control	0.53±0.53	0.8±0.55	1.04±0.53	1±0.53	0.9±0.53
I(Parent)	0.09± 0.11	0.22±0.19	1.01±0.11	0.08± 0.06	0.13±0.50
II(Derivative)	7.32**±7.29	6.32**±3.95	5.85**±5.00	4.82**±5.70	6.00**±2.29
III (Derivative)	2.65**±5.93	3.83*±4.14	3.88**±4.14	4.43**±4.69	4.12**±3.24
IV (Derivative)	0.42*±3.60	0.02*±4.95	0.18*±6.27	2.17*±3.52	3.72**±4.64
V (Derivative)	0.13±4.28	4.55**±5.98	5.33**±6.45	2.70**±4.12	2.43**±4.55
Pethidine HCl	2.26±0.63	3.52±0.46	2.82±0.13	2.57±0.23	1.57±0.2

Activity Key: Significant= * Highly significant= **

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