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LOCAL ANAESTHETIC ACTIVITY OF SYNTHESISED THIAZOLIDINE-4-ONE DERIVATIVES

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ABSTRACT

The synthesis of thiazolidine-4-one derivatives is done from Schiff base in our department of pharmaceutical chemistry. The synthesis of the thiazolidine-4-one derivatives was done according to S.Ramachandran et al. The synthesized four compounds of thiazolidin-4-ones was characterized by IR and ^{1}H-NMR. The synthesized four compounds of thiazolidin-4-ones was subjected to local anaesthetic activity by Infiltration method in guinea pig model which showed good local anaesthetic activity.

INTRODUCTION

Azetidinone and Thiazolidinone derivatives were reported to possess antibacterial[1-3], antifungal[1-3], antitumor[3] antituberculor activity[4], anti-HIV[5], analgesic[6], anti inflammatory[6], and ulcerogenic activity[7]. Isoniazid derivatives were reported to possess antimicrobial[8]activities. Thiazolidine-4-ones derivatives have showed significant local anaesthetic activity[9,10.] Therefore it was envisaged that compounds containing both the chemical moieties would result in compounds of interesting biological activities. In this present study isoniazid were treated with different substituted aromatic aldehydes to produce Schiff base[11]. The Schiff bases were subjected to addition reactions with thioglycollic acid in the presence of 1,4dioxane-anhydrous zinc chloride to produce 4-thiazolidinone derivatives[12]. The Synthesis was done according to S.Ramachandran et al[13.].The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR. The synthesized compounds were screened for local anaesthetic activity by Infiltration method in guinea pig model.[14,15]

MATERIALS AND METHODS

Animals required

Fully grown both sexes guinea pigs (300 to 500 g) were used for the pharmacological studies. The animals were kept under standard conditions (day/night rhythm) 8.00 am to 8.00 pm, 22±2^{o}C room temperature fed, standard pelleted diet (Hindustan Lever, Bangalore) and water *ad libitum*. The animals were housed for one week in polypropylene cages prior to the experiments to acclimatize to laboratory conditions. Guinea pigs were divided into six groups of six in each. Every group was kept in different cages.

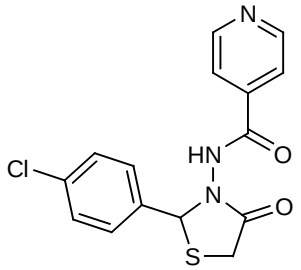
Drugs

The following drugs were used:

Standard -2 % lignocaine (AstraZeneca).

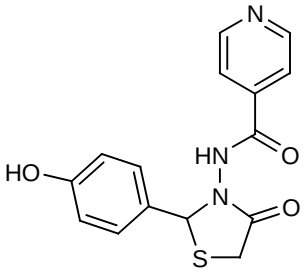
Test compounds 0.1gm of Compounds IVB,VB, VI B, VIIB were dissolved in 2 ml physiological saline.(5% solution)

Compound IV B-N-(2-(4-chloro phenyl) 4-oxo thiazolidin-3-yl) isonicotinamide,



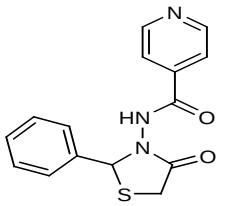
N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)isonicotinamide
Compound IV B

Compound VB-N-(2-(4-hydroxy phenyl) 4-oxo thiazolidin-3-yl) isonicotinamide,



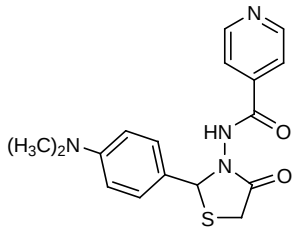
N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)isonicotinamide
Compound Vb

Compound VIB-N-(4-oxo-2-phenyl thiazolidin -3- yl) iso-nicotinamide



N-(4-oxo-2-phenylthiazolidin-3-yl)isonicotinamide
Compound VI b

Compound VII B-N-(2-(4-(Dimethyl amino) phenyl)-4 oxothiazolidin-3-yl) isonicotinamide)



N-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)isonicotinamide
Compound VII b

EXPERIMENTAL PROTOCOL

Intracutaneous wheel in guinea pigs [14-18]

Guinea-pigs of both sexes weighing between 300 and 500g were used. The animals were divided into six animals in each group. On the day prior to the study, the hair on the back of guinea pigs near the midline (four different areas of 4 cm each) were clipped and removed.

Group-I The animals received 0.2 ml physiological saline.

Group-II The animals received in 0.2 ml of 5% Compound IV B in physiological saline.

Group-III The animals received 0.2 ml of 5% Compound V B in physiological saline.

Group-IV The animals received 0.2 ml of 5% Compound VI B in physiological saline.

Group-V The animals received 0.2 ml of 5% Compound VII B in physiological saline.

Group-VI The animals received 0.2 ml of 2% lignocaine hydrochloride.

The test compounds (IVB,VB,VIB,VIIB) and standard drugs were injected intracutaneously in all the groups with equal volumes of 0.2 ml into the shaved areas and wheels were marked with ink and the time of injection noted. The normal responses of the animals were observed first by applying pin pricks in the midline. The painful reaction was observed after pricking 6 times the skin at the center of the wheel (every 5 s) with 5 min intervals during the first 30 min of observation. The responses were recorded up to 30 min. A localized skin twitch, usually accompanied by squeak, was considered as the normal response to pin prick. When the animal failed to respond either by twitching of the muscle or squeaking following a pin pricks, a negative response was recorded.

Infiltration anaesthesia method [14,15]

The infiltration anaesthetic activity was studied by the wheal preparation in guinea pigs by employing the method suggested by Bulbring and Wajda [14] & Chance and Lobstein[15]. The results are computed in Table I and depicted as comparison in Graph 1

Table I- LOCAL ANAESTHETIC ACTIVITY IN GUINEA PIG BY INFILTRATION METHOD

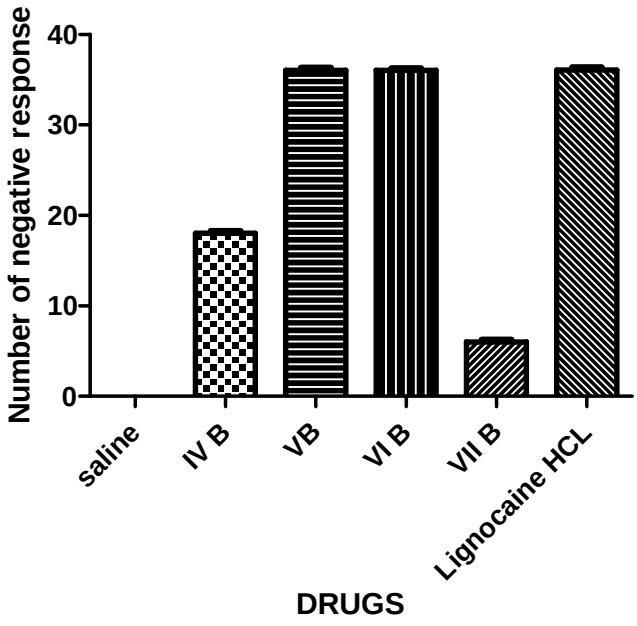
Groups	Drugs	Concentration	Duration of action in minutes							Total Number of negative response
			0	5	10	15	20	25	30	
I	**Physiologicalsaline**	**control**	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0
II	**Compound IVB**	**5%**	0/6	0/6	6/6	6/6	6/6	0/6	0/6	18
III	**Compound V B**	**5%**	0/6	6/6	6/6	6/6	6/6	6/6	6/6	36
IV	**Compound VI B**	**5%**	0/6	6/6	6/6	6/6	6/6	6/6	6/6	36
V	**Compound VII B**	**5%**	0/6	0/6	6/6	0/6	0/6	0/6	0/6	6
VI	**Lignocaine Hydrochloride**	**2%**	0/6	6/6	6/6	6/6	6/6	6/6	6/6	36

Comparisons were made between: Group I, II, III, IV, V and VI.Values are expressed as

0 indicates presence of sensation(squeaking sound)

6 indicates absence of sensation(squeaking sound)

Graph I : COMPARISON OF NUMBER OF NEGATIVE RESPONSES VS DRUGS USED



RESULTS AND DISCUSSION

INFILTRATION ANESTHETIC ACTIVITY

The synthesis of thiazolidin-4-one derivatives is done from Schiff base in our department of pharmaceutical chemistry[13]. The synthesized four compounds of thiazolidin-4-ones was characterized by IR and NMR. The synthesized four compounds of thiazolidin-4-ones was subjected to local anaesthetic activity by Infiltration method in guinea pig model[26].

The compound IV B at 5% concentration showed an onset of action at 10mts and duration of action of 10mts. The compound V B at 5% concentration showed an onset of action at 5mts and duration of action of 25 mts. The compound VI B at 5% concentration showed an onset of action at 5mts and duration of action of 25mts. The compound VII B at 5% concentration showed an onset of action at 10mts and showed shorter duration of action .The lignocaine hydrochloride at 2% concentration showed an onset of action at 5mts.

The compound IV B and VII B showed the response and having a shorter duration of action when compared with the standard.

The compound V B and VI B has good response and having longer duration of action when compared with standard.

CONCLUSIONS

The present study discloses that the Local anesthetic action on Guinea Pig where the group III and IV (compounds VB and VIB) showing positive response, i.e. there is loss of sensation and the duration of action is longer, and the group III and IV(compounds IVB and VIIB) showing a negative response, i.e. there is no loss of sensation and the duration of action is shorter, when compared with the standard drug. Thus the test compound V B and VI B showing significant local anaesthetic activity. Therefore it is suggested to synthesise more compounds in this series and evaluate there pharmacological actions.

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