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CNS DEPRESSANT, ANALGESIC AND ANTIINFLAMMATORY ACTIVITY OF CERTAIN OXANILAMIDE DERIVATIVES

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The present study was designed to evaluate the CNS depressant, analgesic and antiinflammatory activity of six N- {D-threo(-)-1-(p-nitrophenyl)-1,3-dihydroxyisopropyl} -N-4-substituted carbamyol-3-hydroxyoxanilamides. The CNS depressant activity of these compounds was evaluated by measuring their effects on the spontaneous motor activity of mice using the actophotometer technique, while the analgesic activity was evaluated by means of the writhing method. The antiinflammatory response was measured in rats by the trypan blue method. Aspirin was used in these experiments as a reference drug for comparative purposes. This study revealed that the compounds in question possess certain degree of CNS depressant and analgesic activity comparable but less than that of aspirin. Variable degrees of antiinflammatory activity were observed and the effectiveness of some of these compounds was almost comparable to that of aspirin.

The possible correlation between the chemical structure and pharmacological activity was proposed.

Previous studies have shown that salicylates are still the primary drugs used for treatment of various rheumatic conditions [1,2]. No other drug of the group is superior in its analgesic, antiinflammatory and antipyretic properties.

The other substituents are only used if salicylates proved to to be ineffective or can not be given[1].

Recently a number of oxanilic acid amide derivatives were found to possess antiinflammatory property that exceeds that ofmefenamic acid and with a greaterr reduction of their acute toxicity[3]. Moreover, a number of N,N'-oxamides were synthetized and were found experimentally to possess a marked antiinflammatory and less toxic effect in comparisons to aspirin[4]. These findings have encouraged us to evaluate the CNS depressant, analgesic and antiiflammatory effects of a group compounds that were synthetized at the pharmaceutical chemistry department of our University.

EXPERIMENTAL

Materials:

Compounds under investigation were prepared at the department of Pharmaceutical chemistry, Assiut University[5]. These compounds and their chemical structures are listed in Table(1).

The chemicals used are: Acetylsalicylic acid (El-Nasr Co,), histamine phosphate (Merck Sharp Co.,), trypan blue and p-benzoquinone (Prolabo Co.),

Animals used:

Adult albino rats (150-200 gm) and adult albino mice(20-30 gm) of either sex were supplied locally.

Evaluation of CNS depressant activity:

The CNS depressant activity of the compounds in question was evaluated by measuring their effects on the spontaneous motor activity of mice. The actophotometer technique was employed for this purpose[6] in which a light beam is interrupted whenever the mouse crosses its path. Groups of adult

albino mice of either sex were used and each was intraperitoneally injected with 50 mg/kg of each of the tested compounds suspended in 1% carboxymethylcellulose(CMC) solution. Besides, two groups served as control, one was saline treated and the other was injected with 1% CMC solution. In addition, another group was injected intraperitoneally with 50 mg/kg of aspirin suspended in CMC. Each mouse was placed in the actophotometer and a 5 minutes-count was taken before treatment and 30, 60 and 90 minutes after. The percentage decrease in the normal spontaneous activity was determined and compared with the control group.

Evaluation of Analgesic Activity:

Compounds were tested for analgesic activity, in comparison with aspirin, by the writhing method in mice[7]. Suspension of tested substances and aspirin were intraperitoneally injected into mice. After 30 minutes an intraperitoneal injection of 0.25 ml of 0.02% solution of p-benzoquinone was given and animals were observed for writhing during a period of one hour. Groups of 10 mice were used for each does level and the median effective dose (ED 50) i.e. the dose preventing writhing in 50% of animals and its 95% confidence limits were calculated for each compound by the method of Litchfield & Wilcoxon[8].

Evaluation of Antiinflammatory Activity:

Antiinflammatory activity was determined by the trypan blue method[9]. This method depends on the quantitative determination of the effects of the drugs under investigation

on the rate of capillary permeability disturbance caused by the intradermal injection of a phlogogenic substance such as histamine. The rate of capillary permeability was calculated as the time taken for the appearance of the blue colour around the sits of the intradermal injection of histamine phosphate (0.02 ml of a 1% solution) following an intravenous injection of 2 ml/kg of a solution of trypan blue dye.

Suspensions of the tested compounds as well as aspirin were intraperitoneally injected into rats in two dose levels (50 mg and 100 mg/kg) and were evaluated for their antiinflammatory activity after 30 minutes following injection. Control animals were treated in the same manner after an intraperitoneal injection of a 1% suspension of CMC.

RESULTS AND DISCUSSION

The results presented revealed that a significant reduction in the spontaneous motor activity following the injection of each of the tested compounds and aspirin (Table 2). This might reflect the action of these compounds on the various levels of the CNS responsible for initiation and coordination of locomotion [10]. Table 2 also shows that the response was prominent 30 minutes following the injection. Moreover, at each time period the magnitude of aspirin response was found to be much greater than with any of the tested compounds. This indicates the weak CNS depressant effects of these compounds in relation to aspirin. For comparative purposes among the six different compounds, the response observed following 30 minutes will be considered. Thus compound

IX d appears to be the most potent while IX g the least potent of the group. In general compounds IX a, IX b and IX d have a much greater potency than those designated IX e, IX f and IX g. This indicates that the activity increases with increase of the carbon chain substituent up to three carbon atoms. Further increase in the number of carbon atoms (IX f) or branching of side chain (IX e, IX g) reduces the activity.

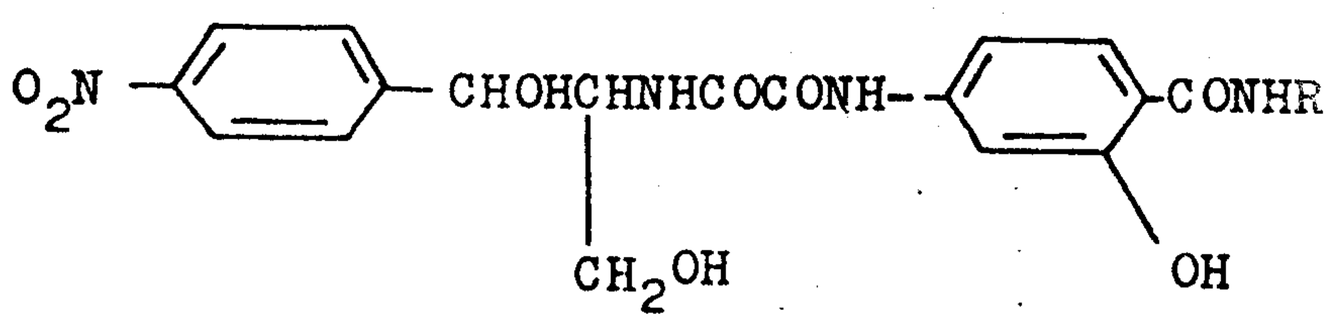
In studying the analgesic activity of the investigated compounds (Table 3), variable responses have been obtained. However, the pattern of response obtained with CNS depressant activity is parallel to that of analgesic activity. The concept of a central antinociceptive component to the analgesic action of the non-narcotic analgesic is documented in the literature [11,12] and is supported recently by the work of Dubas and Parker[13]. However, within the last decade a convincing evidence of the peripheral action of such analgesics has been presented that involves a response on the endogenus mediators of inflammatory reaction[14].

Regarding the antiinflammatory activity of the tested compounds, Table 4 and Fig. 1 show that the response is more manifested following large (100 mg/kg) rather than small doses (50 mg/kg). With the large dose level it is clear that 5 compounds possess certain degree of antiinflammatory activity while compound IX g is devoid of any activity compared to control. The effectiveness of some of these compounds was almost comparable to that of aspirin viz, IX b and IX d are equipotent with aspirin. Comparing the structure with activity it can be shown that the presence of alkyl group substituents with three carbon atoms is optimal

for activity. Increasing the number to four acarbon atoms in a straight chain reduced the activity while if the chain is branched the activity is lost. The proved antiinflammatory activity of the investigated compounds has led to the suggestion that these compounds might suppress the effect of histamine on vascular permeability as indicated by the experimental studies which demonstrated the antiallergic activity of certain oxanilic acid esters[15]. Moreover, the activity of some of these chemically related compounds was found to be more superior than that of disodium cromoglycate[15]. The antagonistic activity of these compounds to the other endogenous substances that might be involved in inflammatory reactions can not be precluded, since the antiasthmatic activity of oxamoyl moiety-containing compounds was experimently documented in rate[16].

As evidences are accumulating to explain analgesic and antiinflammatory activity of these compounds in terms of predominently peripheral action on autacoid release, a more through investigation of the compounds in question needs to be conducted to elucidate the possibility of such a response.

Table 1 : Chemical structure of the six oxanilamide derivatives under investigation



Compound	*R*
IX a	H
IX b	$-CH_2CH_3$
IX d	$-CH_2CH_2CH_3$
IX e	$-CH(CH_3)_2$
IX f	$-CH_2.CH_2.CH_2.CH_3$
IX g	$-C(CH_3)_3$

Table 2 : Effect of oxanilamides (50 mg/kg) on the spontaneous motor activity of mice.

Treatment	*% decrease in spontaneous motor activity of mice after*		
	30'	*60'*	*90'*
Saline	29.65±1.30	56.88±3.84	61.65±3.13
1% CMC	31.42±2.20	54.60±2.64	63.22±3.02
IX a	52.50±2.76*	63.90±2.91	71.73±2.75
IX b	53.20+2.11*	67.40+3.30	70.45+2.12
IX d	60.60±4.49*	66.98±4.60	71.60±2.95
IX e	47.80±3.97*	64.90±6.00	70.75±3.40
IX f	45.90±3.78*	54.50±5.00	68.20±3.19
IX g	42.88±7.75*	53.85±4.30	66.73±6.30
Aspirin	65.80±3.38*	70.76±3.94*	73.8±2.97*

Data represent mean + S.E of 6 observations

* : Significant result at $P < 0.05$

Table 3 : Median effective (analgesic) doses (ED50) of the oxanilamides (IX) in comparison with aspirin.

Compound	*ED 50 and its confidence limits (mg/kg)*
Aspirin	80 (64-100)
IX a	130 (87.8-192.4)
IX b	110((66.6-181.5)
IX d	105 (65.6-168)
IX e	140 (90.3-217)
IX f	150 (88.2-255)
IX g	200 (114.3-350)

Table 4 : Antiinflammatory action of the oxanilamides against inflammation induced by histamine

Compound	*Time (minutes) taken for appearance of the blue colour around the histamine wheat*	
	50 mg/kg	*100 mg/kg*
Control (1% CMC)	2.04±0.07	2.04±0.07
Aspirin	2.84±0.06*	3.28±0.05*
IX a	2.39±0.06*	2.87±0.24*
IX b	1.96±0.10	3.40±0.26*
IX d	2.17±0.18	3.10±0.15*
IX e	2.08±0.17	2.67±0.10*
IX f	2.25±0.17	2.50±0.11*
IX g	1.90±0.16	2.25±0.15

Data represent mean±S.E of 10 observations

* : Significant result at $P < 0.05$.

CNS depressant, analgesic and antiinflammatory activity of certain oxanilamide derivatives

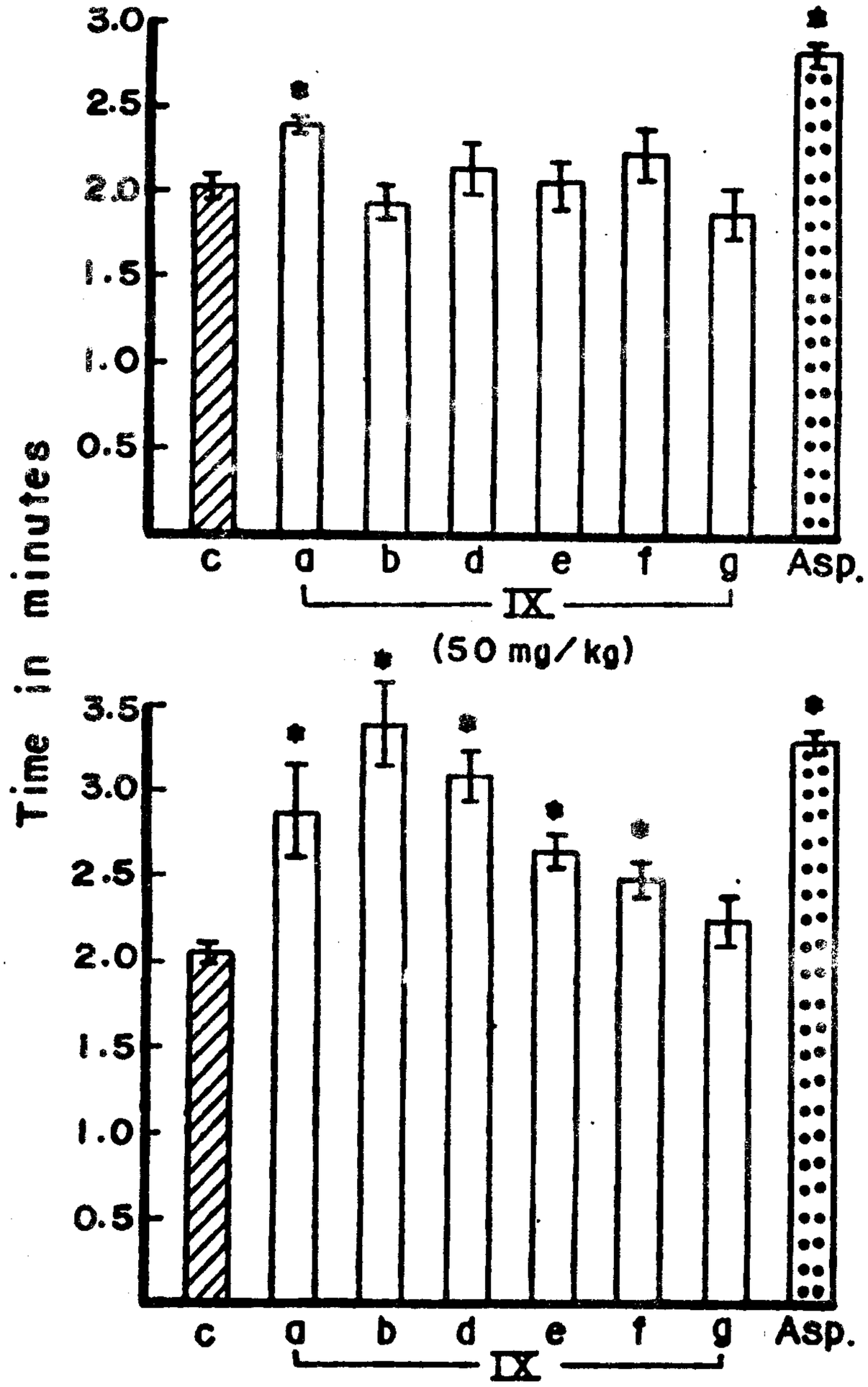


Fig.(1): Antiinflammatory activity of 50 and 100mg/kg of oxanilamide derivatives against inflammation induced by histamine in rats.
(c_control ; IX a_g_oxanilamides ;
Asp_aspirin ; * Significant results at P<0.05)

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التأثيرات المثبطة للجهاز العصبى المركزى والمسكنة للالم والمضادة للالتهابات لبعض اميدات الاوكسانيل

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لقد اوضحت نتائج هذه الدراسة ان لهذه المركبات تاثير مثبط للجهاز العصبى المركزى كما أن لها تاثير مسكن للالم ولكنه غير مقنع مقارنة بالاسبرين اما تأثيرها المضاد للالتهابات فقد اثبتت الدراسة فاعلية هذه المركبات حيث وجد ان بعض منها لها تأثير مقارنة بالاسبرين.

وقد تمت فى هذه الدراسة مناقشة العلاقة بين التأثير الفارماكولوجى لهذه المركبات وتركيبها الكيميائى.

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