ANTIINFLAMMATORY ACTIVITY OF N-ARYLPHTHALIMIDES.

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ABSTRACT

N-Substituted phthalimides are an interesting class of compounds with antiinflammatory activity and other activities. In this work, the acute anti-inflammatory property of *N*-phenylphthalimide **(a)**, *N*-(2-nitrophenyl)phthalimide **(b)**, *N*-(4-bromophenyl)phthalimide **(c)**, and *N*-(4-chlorophenyl)phthalimide **(d)** has been determined. The acute antiinflammatory activity was evaluated by the carrageenin-induced edema. The best antiinflammatory activity was found with *N*-(2-nitrophenyl)phthalimide at a dose level of 250 mg/kg, and it was similar to aspirin and to ibuprofen. The other *N*-arylphthalimides also reduced edema in mice, but the results were not significant. We conclued that *N*-(2-nitrophenyl)phthalimide may have a future as a new anti-inflammatory agent.

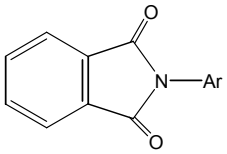
Introduction

The inflammatory process involves a series of events that can be elicited by numerous stimuli (e.g., infectious agents, ischemia, antigen-antibody interaction and thermal or other physical injury). At a macroscopic level, the response usually is accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia) and pain.[1] Inflammatory response occur in three distinct phases, each apparently is mediated by a different mechanism; an acute transient phase, characterized by local vasodilatation and increased capillary permeability; a delayed subacute phase most prominently characterized by infiltration of leukocytes and phagocytic cells; a chronic proliferative phase showing tissue degeneration and fibrosis.[2]

The prostaglandins were particularly associated with the development of pain that accompany lesion or inflammation.[1] Non-steroidal antiinflammatory drugs (NSADs) are widely used for different inflammatory disorders.[4] These drugs exert their antiinflammatory effect by inhibition of the enzyme cycloxygenase (COX). This mechanism is the basis for their therapeutic effect as well as their toxicity.[3] Gastrointestinal irritation, ulceration and haemorrhage; fluid retention, exacerbation of hypertension, and exacerbation of bronchopasm and anaphylaxis are their most serious adverse effects, although many others have been recorded.[5]

Some *N*-substituted phthalimides have interesting biological activities, such as, hypolipidemic[6], anticonvulsant[7], antiviral[8], analgesic[9] and antiinflammatory[10] .

The aim of this work was to evaluate whether *N*-phenylphthalimide **(a)**, *N*-(2-nitrophenyl)phthalimide **(b)**, *N*-(4-bromophenyl)phthalimide **(c)**, and *N*-(4-chlorophenyl)phthalimide **(d),** have *in vivo* antiinflammatory activity (Scheme 1).



Ar
a: Ph
b: 2-NO_2Ph
c: 4-BrPh
d: 4-ClPh

Scheme 1

Experimental

- *Animal*

Three month-old Swiss white mice with 25 to 30g body weight were maintained with water and food (Labina – Agribands of Brazil Ltda.) *ad libitum*. Groups of 10 animals were used in the experiment.

- *Drug administration*

The drugs used were **a-d** and phthalimide. All compounds were suspended in aquous solution of 1% carboxymethylcellulose and administered intraperitoneally, in the morning[11]; at a single dose of 250 mg/kg/day. Other group received only 1% carboxymethylcellulose.
Two positive and one negative antiinflammatory tests were done in three groups by intraperitoneal administration of 250 mg/kg of aspirin (standard for pharmacological comparative test[1]), 250 mg/kg of ibuprofen (Laboratory Teuto Brazilian Ltda. - Brazil) and 0.9% of aqueous saline solution, respectively.

- *Acute anti-inflammatory activity*

The anti-inflammatory activity was determined by Levy`s method[12]. 0.1 ml of 1% carrageenin (Sigma, St. Lousis, USA) in 0.9% NaCl was injected through the plantar tissue of the right hind paw of each mouse to produce inflammation. After four hours, their paws were cut and weighed. The results were analysed according to percentage of inflammation reduction, as descibed afterwards.[14]

- *Statistics*

The results for antiinflammatory activity were expressed as mean ± S.D., and the significance of the difference between the control and test groups was evaluated by the Student ´t`test for independent samples. In all, $p<0.05$ was used as the criterion of statistic significance.

Results and Discussion

The acute toxicity study using phthalimide itself and its four aryl derivatives indicated that the dose (250 mg/kg) required for antiinflammatory activity was in the safe therapeutic range. The LD_{50} was >2 g/kg. Phthalimide and compound **a** reduced the carrageenin-induced edema by 17% and 18%, respectively. The reduction was significant ($p<0.05$) (Table 1) when a comparison was made with the control group.

Table 1. Comparision of the antiinflammatory activity of compounds **a-d**.

Compound	Dose (mg/kg)	Avarage Paw Weight (g)	Inhibition (%)
Control (saline)	-	0.1530	-
Aspirin	250	0.0651***	58
Ibuprofen	250	0.0558**	66
CMC	-	0.1458	5
Phthalimide	250	0.1247*	17
a	250	0.1285*	18
b	250	0.0446**	67
c	250	0.1211*	22
d	250	0.1024**	32

Significant differences: *p<0.05; **p<0.005; ***p<0.001.
CMC : carboxymethylcellulose.

The compound **c** reduced the edema by 22%. Compound **d** reduced the edma by 32%. However, when the hydrogen atom was substituted by a nitro group in the *ortho* position of the phenyl ring giving **b**, the anti-inflammatory activity increased by 67%, and it was significantly ($p<0.001$) different from the groups treated with saline or 1% carboxymethylcellulose (Table 1). Furthermore, the antiinflammatory effect of compound **b** was similar to that obtained with aspirin and ibuprofen (Table 1).

Conclusion

The results indicate that the phthalimide derivative a, b, c and d are able to reduce the

carrageenin-induced edema in mice. The anti-inflammatory effect of N-(2-nitrophenyl)phthalimide are similar to that obtained with the commercial available drugs aspirin and ibuprofen.

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