A Comparison of the Anti-Inflammatory Effects of Copper Aspirinate and Other Copper Salts in the Rat and Guinea Pig

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Abstract

A comparison of the anti-inflammatory (AI) activity of copper compounds in models of kaolin-induced paw oedema and u.v. erythema in the rat and guinea pig is described. The results demonstrated considerable species variation, the guinea pig being more sensitive to the AI and irritant effects of copper aspirinate and the other copper compounds. The route of administration of these compounds was also an important factor in interpreting AI activity obtained. Indeed, the counter-irritation effects of the copper compounds may be largely responsible for the AI activity obtained after subcutaneous administration.

The comparison between copper aspirinate and aspirin, performed in order to determine whether a copper complex of an AI drug was more active than the parent AI compound, failed to produce a clear difference in activity although copper aspirinate was more effective than aspirin in certain cases.

It is concluded that this study highlights the complexities of copper therapy against inflammatory processes and furthermore indicates the importance of species, the model of inflammation and route of drug administration in interpreting data obtained with copper containing compounds.

Considerable interest has centred recently on the anti-inflammatory (AI) activity of copper salts [1-5]. The claim has been made that the copper salts of a variety of ligands including anti-inflammatory drugs (AID) possess AI activity greater than the ligand itself [1]. This effect has been attributed to non-specific tissue irritation which elicits a counter-irritation phenomenon [3]. The observation that copper complexes of certain AID, including aspirin, reduced gastric side effects of the AID produced in the rat [1] has been verified by others [5].

The rat has been used almost exclusively for these studies and since species differences in the AI potency and gastric irritancy of AID have been reported [6] we have compared the AI activity of copper compounds in the rat and the guinea pig. An indication that differences in the activity of copper compounds between these species might exist came from the observation that simple copper complexes possessed oral AI activity in the guinea pig u.v. erythema model but not in rat kaolin paw oedema [7]. Consequently we have examined the AI activity of a variety of copper compounds in models of kaolin induced paw oedema and u.v. induced erythema in both species. We have furthermore examined the effects of different routes of administration of these compounds in order to establish whether these compounds are likely to be acting directly or indirectly via the counter-irritant phenomenon.

Materials and methods

Male Wistar rats (CE/CFHB, 80–100 g) or female Dunkin Hartley guinea pigs (150–180 g) were used throughout the experiments.

Kaolin paw oedema was produced in the rat as described previously [8]. An equivalent model of kaolin paw oedema was established in the guinea pig after preliminary studies to establish an optimal kaolin concentration, a time course of the oedema and the sensitivity of the oedema to AID. It was decided to routinely evaluate the oedema 4 h after the subplanar administration of 0.1 ml of a 10% w/v suspension of kaolin in 0.9% saline. Inhibition of oedema formation was assessed by comparing the swelling obtained in the treated animals and the controls, and expressed as percentage inhibition.

U.V. erythema was produced in rats using a 90 sec exposure time as described previously [9]. Guinea pigs were treated in similar way except that the animals were exposed to the light source for 120 sec. Inhibition of the erythema was assessed by comparing the erythema obtained in treated animals and the controls, and expressed as a percentage.

Animals treated orally with the compounds under investigation were sacrificed 6 h after administration of the compound and the stomachs were removed for visual
examination. These animals had previously been starved for 18 h although water was allowed ad libitum. The time interval was chosen on the basis of previous observations that indicated that most non-steroidal AID produced marked irritant responses by 6 h (unpublished observations). Gastric irritancy in rats was scored using the following order scale: 0, no effect; 0.5, sporadic haemorrhagic lesions; 1.0, several small lesions; 2.0, large lesions (<5 per stomach); and 3.0 large lesions (>5 per stomach). Stomachs from guinea pigs were assessed using a modification of this scoring system since the gastric lesions were less distinct and far greater haemorrhaging was apparent. The following order score was adopted for the guinea pig: 0, no lesions; 1.0 minor haemorrhaging; 2.0 moderate haemorrhaging; 3.0 severe haemorrhaging. For both species the gastric irritancy score was summed for groups of 5 animals and was converted to a percentage using the maximum score of 15 per group as the 100% value.

All the compounds for both oral and s.c. routes were administered in 5% mulgofen (EL-719, GAF Co., Manchester, England) in distilled water (0.2 ml/100 g body weight).

Results

1. Guinea pig kaolin oedema

Subplantar suspensions of kaolin (5 and 10% w/v) produced dose related oedema in guinea pigs reaching a plateau between 3 to 5 h (Fig. 1). The oedema was still present at 48 h. The effect of several AID on the 4 h kaolin oedema are described in Table 1. The non-steroidal AID, indomethacin and phenylbutazone, effectively inhibit this oedema although they are less effective than in the rat. Moreover, neither drug produced gastric irritation in the guinea pig although considerable irritation was apparent after administration to rats (Table 1). Steroidal AID exhibit only slight AI activity in the guinea pig compared with their potency in the rat.

2. Effect of copper compounds and ZnSO₄ on guinea pig and rat kaolin paw oedema and u.v. induced erythema

Table 2 describes the anti-oedema and anti-erythemic effect of a variety of copper salts and zinc sulphate after oral administration.

The copper salts did not significantly affect the guinea pig paw oedema and only Cu₂O inhibited the rat paw oedema. However, both Cu₂O and CuCl₂ inhibited the guinea pig erythema although none of the copper salts affected the rat erythema response. The copper salts all possessed gastric irritant effects in the

![Figure 1](image-url) Time course of kaolin oedema in the guinea pig.