EVALUATION OF POTENTIAL ANTIINFLAMMATORY ACTIVITY OF COPPER (II) AND ZINC(II) BENZENE-1,4-DIYLBIS(OXYACETATES), FREE BENZENE-1,4-DIYLBIS(OXYACETIC)ACID AND THEIR MIXTURES IN RATS

Tumová, I. – Sokolík, J., – Lacko, I. – Račanská, E.

1Department of Pharmacology and Toxicology and 2Department of Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic

Using rat paw dextran- and/or carageenan-induced edemas, the antiinflammatory activity of copper(II) and zinc(II) benzene-1,4-diylbis(oxyacetates) (complexes 1c and 1z) and free benzene-1,4-diylbis(oxyacetic)acid (1a) and their equimolar mixtures (1cz, 1ac and 12az) were evaluated plethysmometrically. All the tested compounds were administered intraperitoneally in the single dose 50µmol/kg of body weight (calculated for the carboxylate fragment) 30 minutes before injecting the irritant. The antiphlogistic activity of the compounds (expressed as a mean edema reduction) was found as: 1a 27.6 % / -23,0 % < 1c 44.2 % / 34.7 < 1z 69.2 % / 30.3 % < 1cz 59.7 % / 67.0 % < 1ac 53.1 % / 77.6 % < 1az 83.8 % / 85.5 %. The relationships between the coordination-chemical properties and the biological effects on the corresponding compounds are discussed.

Key words: copper(II) and zinc(II) complexes mixtures – rat paw carageenan- and dextran-induced edemas – anti-inflammatory activity

INTRODUCTION

Carboxylatocopper(II) and -zinc(II) complexes seem to be beneficial in suppressing the inflammation and other pathological processes [1-3]. These types of coordination compounds with aryloxyacetate acidoligands possess significant anti-inflammatory activity influencing the experimental rat oedemas [4-6]. In effort to define basic relationship between chemical structure and the biological activity of a relative compounds, assumed antiphlogistic activity of a new group of Cu(II) and Zn(II) complexes with double oxyacetate groups on phenylene moiety has been studied.
EXPERIMENTAL

Benzene-1,4-diylbis(oxyacetic) acid (1a) was prepared according Ettel et al. [7]. Copper(II) benzene-1,4-diylbis(oxyacetate) trihydrate (1c) and dihydrate of zinc(II) salt (1z) were synthesized by reaction of the sodium salt of parent acid with the corresponding metal(II) sulphates as the water insoluble compounds.

Elemental analysis. The acid (1a) – C_{10}H_{10}O_{6} (M_r = 226.19) – calc./found: 53.10/53.29 % C and 4.42/4.50 % H. Complex 1c – C_{10}H_{14}O_{9}Cu (M_r = 341.76) – calc./found: 35.14/34.97 % C; 4.42/4.50 % H and 18.59/18.64 % Cu. Complex 1z – C_{10}H_{12}O_{8}Zn (M_r = 325.57) – calc./found: 36.89/36.97 % C; 3.82/3.80 % H and 20.08/20.27 % Zn.

Coordination compounds prepared belong probably to polymer triaqua[benzene-1,4-diylbis(oxyacetato)]copper(II) and diaqua[benzene-1,4-diylbis(oxyacetato)]zinc(II) complexes with distorted tetragonal or tetrahedral geometry of the central atom (M^{II}) as it was found in Cu(II) complex of the 1,3-derivative [8].

All compounds were dispersed in sterilized saline with the content of 0.05 % Tween® 80 (Merck) by sonication in an ultrasound bath in concentration of 50 µmol/cm^3 (calculated for oxyacetate-fragment). The mixed two-component species (1cz, 1ac and 1az) were prepared by the same above-mentioned procedure from the acid and corresponding complexes in equimolar ratio, i.e. 12.5 µmol/cm^3 for each of them. Wistar male rats (Dobrá Voda, Slovakia) weighting 260 ± 20 g were used.

The acute antiphlogistic activity was measured by the reduction of rat paw edema, induced by an injection of 0.1 cm^3 of 6.0% dextran or 0.1 cm^3 of 1% carrageenan (Serva) in sterilized saline. The tested compounds were applied intraperitoneally, in a single dose of 50 µmol/kg of body weight, 30 min before injecting the irritant substance. The control group (CG) received only a vehicle. The changes of edema volume were evaluated plethysmometrically during period of 180 and/or 360min. respectively [9]. All values are represented as mean (± SEM). Statistical evaluation was performed using the Student’s t-test with statistical significance at p<0.05.

RESULTS AND DISCUSSION

Using rat paw dextran-/carrageenan-induced oedemas the anti-inflammatory activity of copper(II) and zinc(II) benzene-1,4-diylbis(oxyacetates) (complexes 1c and 1z), free benzene-1,4-diylbis(oxyacetic) acid (acid 1a) and their two-component mixtures (1cz, 1ac and 1az) was assayed plethysmometrically (Tables 1 and 2). The average activities of the tested species for both edema types, expressed as a measure of oedema volume reduction, were increasing in order: 1a 27.6 % / -23.0 % < 1c 44.2 % / 34.7 < 1z 69.2 % / 30.3 % < 1cz 59.7 % / 67.0 % < 1ac 53.1 % / 77.6 % < 1az 83.8 % / 85.5 %. It was found that the complexation of benzene-1,4-diylbis(oxyacetato)(2-) with cations Cu^{2+} and Zn^{2+} allowed the enhancement of anti-inflammatory effect in comparison to that of the uncomplexed acid (1a). Thus, Cu(II) and Zn(II) benzene-1,4-diylbis(oxyacetates) and their mixed species with the acid can be advantageous for the controlled liberation
of the corresponding carboxylate and M$^{2+}$ ions acquired for the formation of pharmaco-active entities under in vivo conditions. It seems that the synergistic effect of uncomplexed acid in both examined edema models was exhibited mainly for the mixtures 1az and 1ac. The maximal anti-inflammatory effect have been already developed in 60th min. after administration of compounds and persisted till 180min. when the activity gradually declined (Tables 1 and 2).

Our findings are in good correlation with the similar ones which have been performed previously [10]. The equimolar mixture of structurally relative Cu(II) and Zn(II) complexes of 3,6-dimethylsalicylates was in the carrageenan-induced local inflammation model significantly more antiedematically active in comparison with the free 3,6-dimethyl-salicylic acid.

Table 1. Results of pharmacological screening – dextran-induced edema

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Edema volume changes, $\Delta V$ (± SEM) [cm$^3$] / Edema reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time interval (measured in minutes)</td>
</tr>
<tr>
<td></td>
<td>30th</td>
</tr>
<tr>
<td>CG</td>
<td>0.421 (0.02)</td>
</tr>
<tr>
<td>1a</td>
<td>0.328 (0.03)</td>
</tr>
<tr>
<td></td>
<td>22.1</td>
</tr>
<tr>
<td>1c</td>
<td>0.242* (0.02)</td>
</tr>
<tr>
<td></td>
<td>42.5</td>
</tr>
<tr>
<td>1z</td>
<td>0.176** (0.02)</td>
</tr>
<tr>
<td></td>
<td>58.2</td>
</tr>
<tr>
<td>1cz</td>
<td>0.212* (0.02)</td>
</tr>
<tr>
<td></td>
<td>49.6</td>
</tr>
<tr>
<td>1ac</td>
<td>0.178** (0.01)</td>
</tr>
<tr>
<td></td>
<td>57.7</td>
</tr>
<tr>
<td>1az</td>
<td>0.125** (0.02)</td>
</tr>
<tr>
<td></td>
<td>70.3</td>
</tr>
</tbody>
</table>

CG = control group (n = 12). For the compounds see Experimental. Statistical significance: * p < 0.05, ** p < 0.01, *** p < 0.001 (n = 8)
Table 2: Results of pharmacological screening – carrageenan-induced edema

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Edema volume changes, ΔV (±SEM) (cm³) / Edema reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time interval (measured in minutes)</td>
</tr>
<tr>
<td></td>
<td>30th</td>
</tr>
<tr>
<td>CG</td>
<td>0.190 ± 0.05</td>
</tr>
<tr>
<td>1a</td>
<td>0.243 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>-27.9</td>
</tr>
<tr>
<td>1c</td>
<td>0.172 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>1z</td>
<td>0.190 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1cz</td>
<td>0.052* ± 0.02</td>
</tr>
<tr>
<td></td>
<td>72.6</td>
</tr>
<tr>
<td>1ac</td>
<td>0.086 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>54.7</td>
</tr>
<tr>
<td>1az</td>
<td>0.030* ± 0.02</td>
</tr>
<tr>
<td></td>
<td>84.2</td>
</tr>
</tbody>
</table>

CG = control group (n = 11). For the compounds see Experimental. Statistical significance: * p < 0.05, ** p < 0.01 (n = 8)

The mode of action of the complexes tested is probably similar to that of Cu-based non-steroidal anti-inflammatory drugs with carboxylate moiety and based on inhibition of prostaglandin synthesis via the cyclooxygenase isoenzyme system and/or could be related to the modulation of superoxide dismutation, nitric oxide synthetase, and some immunobiological functions [1,2]. The antioxidant functions both zinc(II) and Zn(II) complexes could be obviously responsible for the protection of protein –SH groups and/or reduction of hydroxyl radical formation from hydrogen peroxide through the antagonism of redox-active transition metals, such as iron and copper [3].

Acknowledgement: This work was supported by the Ministry of Education of the Slovak Republic.
REFERENCES


Registered: May, 2011
Accepted: July, 2011

Doc. RNDr. Ingrid Tumová, CSc.
Faculty of Pharmacy
Odbojárov 10
832 32 Bratislava
Slovakia
tumova@fpharm.uniba.sk
HODNOTENIE POTENCIÁLNEJ PROTIZÁPALOVEJ AKTIVITY KUPRUM(II) A ZINKUM(II) BENZEN-1,4-DIYLBIS(OXYACETATU), VOLNÉJ BENZEN-1,4DIYLBIS(OXYOCTOVEJ KYSELINY) A ICH ZMESÍ U POTKANOV

1Tumová, I. – 2Sokolík, J., – 2Lacko, I. – 1Račanská, E.

1Katedra farmakológie a toxikológie a 2Katedra chemickej teórie liečiv,
Farmaceutická fakulta UK, Bratislava

Protizápalová aktivita kuprum(II) a zinkum(II) benzén-1,4-diylbis(oxyacetátu) (komplexy 1c a 1z) a volná benzén-1,4-diylbi-(octová kyselina) (kyselina 1a) a ich ekvimolové zmesi ( 1cz, 1ac a 1az) bola hodnotená pletyzmometricky na dextranovom, resp. karagenínovom edéme na potkanoch. Všetky testované látky boli podané i.p. v jednorázovej dávke 50µmol/kg telesnej hmotnosti zvierat (počítané na karboxylátový fragment) 30 min. pred injikovaním irritanta. Priemerná antiflogistická aktivita látok (vyjadrená ako miera redukcie edému) bola zistená v tomto poradí: 1a 27.6 % / -23.0 % < 1c 44.2 % / 34.7 < 1z 69.2 % / 30.3 % < 1cz 59.7 % / 67.0 % < 1ac 53.1 % / 77.6 % < 1az 83.8 % / 85.5 %. Diskutujeme vzťahy medzi koordinačno-chemickými vlastnosťami a biologickým účinkom príslušných komplexov