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Effect of two new Synthetic Indole-Containing Derivatives on the Histamine Content of the Conjunctiva

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The aim of the present study was to investigate the effect of two new synthetic indole-containing derivatives C6359 and C6230 (Figure 1) on the histamine content of the rat conjunctiva. This investigation was based on previous reports concerning a) the antiallergic properties of compounds containing the indole ring and b) the reported antidepressive effects of the new compounds, in combination to the effects of fluoxetine on the conjunctival histamine content. The new compounds were administered into the eyes of Wistar rats as follows: a) Groups A-B (n=4-5): 10 µl of 10^{-4} M C6359 into one eye and 10 µl Phosphate Buffer Saline (PBS) into the other (control), b) Groups C-D (n=4-5): 10 µl of 10^{-4} M C6359 into one eye and 10 µl PBS into the control eye, c) Group E (n=3): 10 µl of 10^{-4} M C6359 into both eyes, followed by 10 µl of 100 mg/ml compound 48/80 into one eye and 10 µl PBS into the contralateral eye (control) 15 min after. The animals of groups A, C and E were sacrificed 1 h following administration of the compounds and those of the groups B and D after 24 h. The conjunctiva was removed and the histamine levels were determined fluorophotometrically following extraction of the amine. Statistical evaluation of the results was performed using ANOVA. The studies concerning the recovery of C6359 showed no interference with the assay.

The histamine levels in the conjunctival homogenate 1 h and 24 h after local administration of C6359 were 136.9±8.4 % and 127.5±7.2 % respectively, compared to the control (p<0.03), while those 1 h and 24 h after administration of C6230 were 90.61±2,9 % and 98.3±3.8 % respectively, compared to the control (p>0.05). In group E, the histamine content of the conjunctiva having received compound 48/80 was 77.9±7.35 % compared to the control.

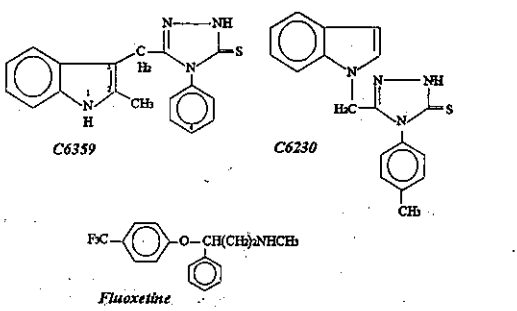

Figure 1. Chemical structure of the two new synthetic derivatives and fluoxetine

The results suggest that the two new products do not directly induce histamine release, at least at the concentration tested, since none of the products resulted in decreases of its levels. However, their action in the conjunctiva varied. The

product C6359, in contrast to C6230 induced increases comparable to those reported for fluoxetine, the selective serotonin reuptake inhibitor (SSRI). The differences in the chemical structure of the two molecules are small (Figure 1). For the identification of structural differences that would account for the action of only one of the products, chemical modelling studies are needed. The fact that the action of the heterocyclic C6359 in the conjunctiva was similar to that reported for the aromatic fluoxetine is of particular pharmacological interest. A primary evaluation of the structure-activity relationship of the two molecules does not, however, reveal any common structural characteristics that would seem responsible for the observed effects. It must be noted that, preliminary behavioural studies have suggested the possible antidepressive action of the product C6359 and, therefore, it deserves further investigation as a SSRI. Finally, the possible SSRI action of the product does not exclude further studies regarding its effect on mast cell degranulation and on the synthesis, release and reuptake of chemical mediators involved in hypersensitivity reactions, such as histamine.