**Effects of Clopidogrel and Fluoxetine on Bleeding Time and Liver When Used Alone or in Combination in Rats**

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Today, prescription of antiplatelet drug with antidepressant drug is increasing because coronary artery disease and depression are co-morbid conditions. Antidepressant SSRIs (selective serotonin reuptake inhibitors) have been thought to have influence on platelet activity because the release of serotonin from platelets is responsible for vasoconstriction and platelet aggregation. A possible drug-drug interaction may be occurred during concomitant use of fluoxetine and clopidogrel. Besides, drug induced hepatotoxicity has also been documented with these two drugs. The present work aimed to investigate the effect of fluoxetine and clopidogrel, alone or in combination, on bleeding time and liver histological patterns.

Male Wistar rats weighing 200-250g (8 rats/group) were administered with 0.5 ml per 100g body weight oral single daily doses of drugs, 20 mg/kg clopidogrel or 10 mg/kg fluoxetine or their combination for a period of four weeks. At the end of the experiments, bleeding time was measured in all groups using an established rat's tail bleeding model. Blood and liver tissue were collected. Hepatotoxic biomarkers including serum levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin (TB) as well as liver histological patterns were evaluated. Data were analysed by ANOVA for normal distribution data and Kruskal-Wallis test for non-parametric data with appropriate post hoc comparisons. Data were expressed as mean ± S.E.M. and acceptable levels of significance were set at p<0.05.

As expected, clopidogrel significantly prolonged the bleeding time when compared with control group (2294.75 ± 686.70 sec vs. 330.75 ± 81.75 sec, p<0.001). Although, fluoxetine modestly increased (not significantly) the bleeding time (339.12 ± 149.97 sec) compared to the control group, surprisingly, treatment with concomitant clopidogrel and fluoxetine significantly exhibited a shorter bleeding time (945.12 ± 263.01 sec) compared to clopidogrel treatment alone (p<0.01). For both clopidogrel and fluoxetine treatment groups, serum ALT and ALP but not TB appeared to be higher in comparison to the control group. However, significant differences could not be detected. On concomitant administration of the drugs, ALT and ALP levels appeared to be higher when compared to the control group or single drug treatment group. The histopathological results also showed adverse alterations in liver morphology in all the treatment groups with increased severity observed in concomitant treatment group.

In conclusion, concomitant treatment with clopidogrel and fluoxetine did not produce additive antiplatelet effect. The attenuation of antiplatelet activity of clopidogrel caused by concomitant administration of fluoxetine could be due to an inhibition of major enzyme, CYP2C19, responsible for formation of active metabolite of clopidogrel. Moreover, hepatotoxicity in the combination group was also increased. Taken together, concomitant use of fluoxetine and clopidogrel should be re-evaluated.