Original Article

Interaction of celecoxib with aspirin

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Objective: To assess the celecoxib interference with the anti-platelet effect of low dose aspirin.

Methodology: We selected eighteen healthy volunteers, aged between 22 and 50 years and allocated them into three groups. After written informed consent the three groups (A,B and C) were given aspirin (10mg once a day), celecoxib (200mg twice a day) and both aspirin and celecoxib each. The drugs were administered for six consecutive days, prohibiting the concomitant use of any other drug. We obtained blood samples from the study subjects on two occasions, before starting drugs and then on the seventh day and analyzed them for platelet aggregation (ADP and collagen induced) and serum thromboxane A2 levels.

Results: If 150mg aspirin is taken daily along with twice daily doses of celecoxib (200mg), aspirin continues to exert an antiplatelet effect. Results show that mean platelet aggregation with ADP was reduced to 60.00±6.19 percent from a baseline value of 83.33±4.77 percent. When collagen was used as a reagent the aggregation of platelets was markedly reduced to 34.50±7.71 from a baseline of 79.17±5.83 percent. Similarly, mean thromboxane B_2 levels reduced markedly from 854.88±51.18pg/ml to 539.94±86.84 pg/ml.

Conclusion: It is safe to use celecoxib with aspirin, as the anti-platelet effect of the latter is not attenuated. (Rawal Med J 202;46:48-51).

Keywords: Non-steroidal anti-inflammatory drugs, aspirin, celecoxib.

INTRODUCTION

Aspirin. A leading drug used worldwide and a common household name.[1] What makes this drug unique is its capability to halt the function of a natural blood cell, the platelet. Synthesis of thromboxane A2 with the consequent impedence of platelet aggregation is the hallmark of low dose aspirin[2]. For this reason it is prescribed to nearly every adult especially those who have or are at a risk of developing cardiovascular disease[3]. Yet there is a problem. The problem is that those being prescribed aspirin in low doses usually also require the use of a non-steroidal anti-inflammatory agent (NSAID) for concomitant ailments.[4] NSAIDs are similar to aspirin in that the target for action of both is the cyclooxygenase enzyme, which is responsible for synthesis of prostaglandins. Inhibition of cyclo oxygenase enzyme (COX) by one drug may influence the inhibition by the other. The action of aspirin is also unique in that the interference in catalytic activity of cyclo-oxygenase is irreversible and permanent, lasting until a new enzyme is synthesized.[5] When low dose aspirin is prescribed for long term use the question arises that if and when a coxib such as celecoxib is co prescribed, will an interaction occur and if it does occur will it interfere with the cardioprotective role of aspirin.[6] In our study we have investigated this very potential interaction and saw how ascertain if the anti-platelet effect of aspirin is hampered due to the concomitant use of the NSAID celecoxib.

METHODOLOGY

The study was conducted in the department of Pharmacology & Therapeutics, Army Medical College and Armed Forces Institute of Pathology, Rawalpindi. Ethics committee of Centre for Research in Experimental and Applied Medicine (CREAM) Army Medical College,Rawalpindi approved the study protocol. By using the non probability convenience sampling technique we conducted this randomized prospective case control study. Our study population comprised of eighteen healthy human volunteers (six females & twelve males) aged 22-50 years, who were within 30% of ideal body weight and had no remarkable medical

history or physical examination. We excluded smokers, those with a known bleeding disorder, drug allergy or a history of any gastrointestinal or cerebrovascular disease. Intake of any other medication during the study period was forbidden and research began after obtaining written informed consent from all participants.[7]

Six study subjects were randomly allocated to one of the three groups. Tab aspirin was obtained from Highnoon Labs Ltd and Getz Pharma was kind enough to provide celecoxib. Both the drugs were taken orally with plain water for six consecutive days. The groups were divided as follows:

Group A: (n=6) Control group, received aspirin 150 mg/day[8]

Group B: (n=6) Celecoxib 200 mg, twice a day[9]

Group C: (n=6) Celecoxib 200 mg 12 hourly and aspirin 150 mg once a day, as above.

Sample for blood analysis was taken on two occasions, i.e. on day zero before any drug intake and secondly, on day seven, 12 hours post consumption of the last dose. Under strict aseptic measures we collected approximately 9ml of blood from the antecubial vein of each subject and poured it in a test tube previously containing 1ml of tri sodium citrate, making the blood anticoagulant ratio 1:10.[7] We used the gold standard method for analyzing platelet function and assessed platelet aggregation by using light transmission aggregometry in platelet rich plasma (PRP).[10]

After confirming availability of Impedence Aggregometer (Model 700, Chrono-Log Corporation, Havertown, PA), samples were taken to Armed Forces Institute of Pathology (AFIP) for analysis. Complete blood count was performed on each sample from which platelet count was assessed. Reassesment of platelet count was then done on the platelet rich plasma (PRP) of these samples, obtained by centrifuging at 1200rpm for 10mins at 37°C. If platelet count was found to be less than 100 x10 per liter, the sample was not used. One at a time, 500 microliters of PRP was pippeted out from each sample and emptied into small cuvettes in which small magnetic stirrers were previously placed. Blood was also centrifuged at 3400rpm for 3 mins in order to obtain platelet poor plasma (PPP).

Chrono-Log Aggregometer Model 700 was used for assessing platelet aggregation. With one sample at a time and bearing PPP as control, we assessed aggregation using two agents i.e., 1µL collagen and 5µL of ADP.[11] From CUSABIO Human Thromboxane A2 ELISA kit was purchased to estimate the levels of this parameter. From each of the samples collected, 1ml of blood was parted and stored at -80°C. Serum from these samples was obtained by centrifuging the samples at 3200rpm for 15mins.[12]

A standard curve was plotted and the concentration of each sample was calculated using this formula.[13]

Total TXA_2 in sample (pg/ml).

$$= \frac{TXA_2 \text{ (pg) in purified sample}}{\text{Volume of sample used for purification (ml)}}$$

Statistical Analysis: Statistical analysis was performed using SPSS version 19 and applied Dependent t-test. Difference between two observations was considered significant if the *p* value was found to be less than 0.05.

RESULTS

Group A: Those individuals who were only consuming low dose aspirin on a daily basis depicted a massive lowering of collagen induced platelet aggregation from 84.16+4.16 percent to 25.50 +5.96 percent (p value of 0.001). Similarly a six day trial of aspirin also reduced the ADP induced platelet aggregation from 85.83+5.23percent to 73.33+3.07 percent (p value 0.03).

Group B: When assessed with ADP, celecoxib was completely insignificant in blocking the aggregation of platelets. This was reflected by a baseline mean platelet aggregation of 82.50±4.42 percent which reached a level of 85.83±7.12 percent (p-value 0.48) after taking celecoxib. For the reagent collagen the results were nearly identical. Six days of consecutive celecoxib consumption caused the mean platelet aggregation of 82.50±4.95 percent to come to a level of 86.67±5.10 percent, giving a p-value of 0.31. The COX-2 selective drug celecoxib displayed effects on thromboxane A_2 levels nearly identical to its influence on platelet aggregation. An insignificant p- value was derived from pretreatment values of 509.39±38.28 pg/ml, which marginally came down to 482.49±30.54 pg/ml.

Table. The comparison of platelet aggregation parameters of Group A, Group B and Group C.

	GROUP A(n=6)		P value	GROUP B(n=6)		P value	GROUP C(n=6)		P value
PARAMETER	**DAY 0**	**DAY 7**		**DAY 0**	**DAY 7**		**DAY 0**	**DAY 7**	
Platelet aggregation with ADP (%) MEAN ± SEM	85.83 ± 5.23	73.33 ± 3.07	0.037	82.50 ± 4.45	85.83 ± 7.12	0.48	83.33 ± 4.77	60.00 ± 6.19	0.01
Platelet aggregation with collagen (%) MEAN ± SEM	84.16 ± 4.16	25.5 ± 5.96	0.001	82.50 ± 4.95	86.67 ± 5.10	0.31	79.16 ±5.83	34.50 ± 7.71	0.00
Thromboxane B2 Levels (pg/ml) MEAN ± SEM	781.11 ±51.39	390.21 ± 34.09	0.00	509.39 ±38.28	482.49 ±30.54	0.09	854.88 ±51.18	539.94 ±86.84	0.02

GROUP C: According to our results the selective COX 2 inhibitor celecoxib doesn't compromise the cardio protective role of aspirin. Six consecutive days of twice daily celecoxib in combination with low dose aspirin were taken by the study subjects. Mean platelet aggregation with ADP reduced from a baseline of 83.33±4.77 percent to a level of 60.00±6.19 percent. Likewise, the mean platelet aggregation with collagen decreased from 79.17±5.83 percent to 34.50±7.71 percent. The p-value with both reagents was calculated to be highly significant, i.e. a value of 0.01 with ADP and 0.00 with collagen.

DISCUSSION

Previous research has shown that aggregation induced by collagen is only partially dependent upon cyclo oxygenase and that, probably, aspirin is also capable of halting platelet function by way of certain non COX1 pathways.[14] Leese and colleagues demonstrated statistically insignificant reductions in platelet aggregation and thromboxane B_2 levels with celecoxib, even at supratherapeutic doses.[15] In a related study conducted by Schwartz and friends, it was concluded that celecoxib and other COX 2 selective agents have no momentous effect on systemic thromboxane B_2.[16] Lee and colleagues demonstrated that if platelet aggregation with ADP and collagen were considered as indicators of platelet function, neither was affected by using celecoxib along with aspirin.[17] Platelet aggregation (with ADP and arachidonic acid) and thromboxane A2 levels both were assessed by Renda and his colleagues to reach the conclusion that aspirins COX 1 activity is not undermined by combining with aspirin.[18] Wilner and friends too explored this interaction with a nearly similar study protocol as ours. Results in this case, too, were identical, i.e. no change in aspirins effect on platelet aggregation (with collagen/ADP) or thromboxane A2 levels due to celecoxib.[19] Infact Bum-Kee Hong showed that celecoxib can even be used safely on top of dual anti platelet therapy, aspirin and clopidogrel.[20] Studies carried out on canines by Lauver however show opposite results, i.e. blockage of aspirins antiplatelet effect when combined with celecoxib.[21]

CONCLUSION

We conclude that if any non-steroidal anti-inflammatory agent needs to be prescribed to an individual who is already taking low dose aspirin, celecoxib is a safe and preferred agent.

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