

The effect of nisoldipine on platelet aggregation

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platelet aggregation induced by ADP, collagen and adrenaline were monitored in 20 hypertensive patients using nisoldipine a calcium channel blocker. Maximum percentage of aggregation in response to adrenaline was decreased at first month on nisoldipine therapy compared with values before therapy but any significant difference was not observed in response to ADP and collagen. These results indicated that the therapy with nisoldipine may be useful for the prevention and/or treatment of thrombotic disorders in patients with hypertension and ischemic heart disease.
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Key Words: Nisoldipine, ADP, Collogen, Adrenaline, Platelets

An increase of intracellular calcium concentration, due either to transmembrane influx of extracellular calcium or to release of plasma membrane bound calcium, is essential to trigger calcium dependent reactions leading to intraplatelet arachidonic acid metabolism activation and platelet aggregation (1,2). The widely employed calcium channel blockers diltiazem, nifedipine and verapamil have been demonstrated to inhibit platelet aggregation induced by various aggregating agents probably through inhibition of intraplatelet calcium mobilization (2-5). In the present study, we evaluated the in vitro effects of recently introduced calcium antagonist, nisoldipine (dihydropyridine calcium antagonist) on platelet aggregation (3,6).

MATERIALS AND METHODS

Blood was obtained after informed consent from 20 hypertensive (mean duration 4year) patients (8 males and 12 females) aged 32-67 (mean 52.50±3.22 year) Criteria for the selection of those to be tested were; no history of hypersensitivity to any substance; of alcohol, drug, or substance abuse; or of any type of bleeding disorder; no known anticoagulant medication and otherwise normal physical examination. The collection of the blood for determining the platelet aggregation

was carried out before and after 4 weeks treatment with nisoldipine 5 mg. twice daily. The patients did not take drug before the two weeks preceding the study.

Following the overnight fasting period, blood was taken from the antecubital vein with a plastic syringe, instantly mixed with a one-tenth volume of 3.8% trisodium citrate and centrifuged (1000 rpm, 10 min) to give the platelet rich plasma (PRP). The remaining blood was further centrifuged at 5000 rpm for 10 min to give the platelet poor plasma (PPP). The platelet count of PRP was adjusted to about 250000±500000 cells/uL plasma by dilution with PPP. Platelet aggregation was measured at 37 °C using a lumi-dual aggregometer (Chrono-log Corporation, Model 450) according to the Sigma Protocol (Sigma Diagnostics, Procedure No: 885). The final concentration of aggregating agents as follows;

ADP (adenosine di phosphate): 20 uM

Collagen: 0.2 mg/ml

Adrenaline: 10 uM

The Chrono-log Lumi-Aggregometer automatically sets the PRP baseline to 90 on the chart recorder when the PRP blank is set to 10. This allows the % aggregation to be calculated from the final chart reading (CR) as follows;

% aggregation= $90 - CR / 90 - 10 \times 100$

The results are expressed as mean values ± standart error. Statistical analysis carried out by Wilcoxon method. A value of p<0.05 was considered significant.

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Table 1. Maximum aggregation percentages induced by all aggregating agents before administration of nisoldipine and one month later on the therapy.

	Before the drug administration	After the drug administration	P value
ADP (20 fM)	62.50±5.27	60.05±3.80	>0.05
Collagen (0.2 mg/ml)	61.76±2.85	58.75±3.65	>0.05
Adrenalin (10 fM)	62.75±3.87	56.82±4.28	<0.05

RESULTS

In hypertensive patients, maximum aggregation percentages induced by ADP before administration of nisoldipine and one month later on therapy with nisoldipine were found as 62.50±5.27 and 60.05±3.80 respectively. There was no significant difference between them ($p>0.05$). Maximum aggregation percentage induced by collagen before the therapy and one month later were found as 61.76±2.85 and 58.75±3.65, respectively. There was no significant difference between them ($p>0.05$). And finally, maximum aggregation percentage induced by adrenaline before administration of nisoldipine and one month later on therapy with nisoldipine were found as 62.75±3.87 and 56.82±4.28 respectively. This inhibition induced by adrenaline was found statistically significant ($p<0.05$). All values are shown in Table 1.

DISCUSSION

In this investigation we found that nisoldipine on therapeutic doses were effected platelet function by inhibiting platelet aggregation induced by only adrenaline. The mechanism of this inhibition remain controversial.

Platelet activation is an essential element in development of atrial thrombosis, and calcium plays an integral role in platelet activation and aggregation (7). All three major classes (dihydropyridines, phenyl alkylamines, thiazepinones) of calcium antagonists have been shown to inhibit platelet aggregation in vitro (2,3,8,9); in contrast some investigators reported no inhibition (10).

At variance with smooth muscle cells and several other cell types, platelets are not provided with voltage operated channels, therefore the inhibition of platelet aggregation by calcium channel blockers may be due to interaction with transmembrane calcium influx through receptor operated channels, or to inhibition of membrane bound calcium mobilization, or to synergism with endogeneous antiaggregatory substances, or to altered mobilization of integral calcium stores, to the inhibition of 5- hydroxytryptamine (5HT) uptake or to calcium independent mechanism (7,11-13). In some studies, the antiaggregatory effects of calcium channel blockers have been shown probably through inhibition of intraplatelet calcium mobilization (1).

Diltiazem may clinically exert an anti-platelet action through the effects of its basic metabolites; however it has been reported that clentiazem is a more powerful platelet inhibitor than diltiazem and the inhibitory effects of two agents were enhanced in the presence of aspirin (14-16).

The studies with nisoldipine are limited and argumentative as well. Orchard et al. have first reported that nisoldipine does not effect aggregation induced by adrenaline or ADP. Whereas Rostagno et al. have shown that nisoldipine can inhibit platelet aggregation like other calcium antagonists (1,17). In an other study, Mehta et al. have reported that abrupt withdrawal of nisoldipine treatment may be associated with precipitation of severe myocardial ischemia (18). The increase in platelet aggregability in vitro in their study have depended on the increase in the affinity of platelet α_2 adrenoceptors for agonist adrenaline. Hollister et al. showed that exposure of platelets to physiologic concentrations of adrenaline reduces in vitro aggregatory response to adrenaline (6). Nisoldipine is known as the most potent agent in inhibiting vascular α_2 adrenoceptors (18). It may be postulated that similar to platelets, human vascular α_2 adrenoceptors also become more sensitive to circulating concentrations of adrenaline after long-term therapy with nisoldipine. The greater inhibitory activity on adrenaline induced platelet aggregation of nisoldipine may be due to the α_2 adrenergic inhibiting activity of nisoldipine as in case of verapamil and diltiazem.

In vitro findings suggest the potential benefit of calcium antagonists in the treatment of human atherosclerosis. A definitive comparison of efficacy and mechanisms between the various substances has not yet been made. The routine treatment of hypertension with a compound like nisoldipine that lowers blood pressure and inhibits platelet activation may be of clinical benefit in patients with ischemic heart disease and hypertensive patients.

Trombosit agregasyonuna nisoldipin'in etkisi

ADP, kollojen ve Adrenalinin neden olduğu trombosit agregasyonu bir kalsiyum kanal blokörü olan nisoldipin kullanılarak, 20 hipertansif hastada takip edildi. Adrenalin cevaptaki agregasyonu maksimal

yüzdesi tedavi öncesi değerlerle karşılaştırıldığında nisoldipin tedavisinin birinci ayında azaldı, ancak ADP ve kollajene olan cevapta kayda değer farklılık gözlenmedi. Bu sonuçlar, hipertansiyonlu hastalardaki trombotik bozuklukların önlenmesi ve/veya tedavisinde nisoldipinle tedavinin yararlı olabileceğine işaret etmektedir. [Turk J Med Res 1995, 13(5):174-176]

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