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In vivo Effects of Ibuprofen and Naproxen on the Plasma Concentration of Diltiazem in Rabbits

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Abstract: An *in vivo* study has been carried out to evaluate the influence interaction of ibuprofen and naproxen on the plasma concentration of diltiazem in rabbits. The study has bee carried out by UV Spectrophotometric method. It has been found that the concurrent administration of diltiazem and ibuprofen has no effect on plasma concentration of diltiazem in rabbits. But concurrent administration of diltiazem and naproxen causes a significant decrease in plasma concentration of diltiazem. These results indicate that great care and monitoring is to be practiced during concurrent administration of diltiazem with naproxen to avoid untoward pharmacological and therapeutic actions related to drug-drug interactions.

Key words: Ibuprofen, naproxen, diltiazem, plasma concentration, rabbit

Introduction

Diltiazem is a calcium channel blocker, which has gained increasing acceptance in the treatment of angina pectoris, hypertension and cardiac arrhythmia (Carlsted and Stanazek, 1990; Martin, 1987). Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) which is used for the treatment of sign and symptoms of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and other non rheumatoid arthropathies, non-articular rheumatic conditions, soft tissues injuries, dysmenorrhoea and dental pain. Naproxen is also a nonsteroidal anti-inflammatory drug which is used for the treatment of sign and symptoms of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, Juvenile rheumatoid arthritis, acute gout, acute musculoskeletal disorders, dysmenorrhoea, Febrile conditions and migraine (Martindale, 1993; Gennaro, 1990).

Dargie *et al*. (1981) studied the interaction between nifedipine nd propranolol in a double blind clinical trial that included sixteen patients with chronic stable angina triggered by exertion. Both frequency of chest pain and nitroglycerin consumption wa significantly reduced by each of the active drugs and their combination added significantly to the effectiveness. Lever *et al*. (1984) studied the influence of diltiazem on the bronchodilator effect of salbutamol in ten male asthmatic volunteers. The result suggests that diltiazem prolongs the bronchodilator action of salbutamol *in vivo*. Van Lith and Appleby (1985) studied the quinidine-diltiazem interaction. They found that the dose-related increase in quinidine serum concentrations are significantly suppressed by concurrent diltiazem therapy. Hamann *et al*. (1987) evaluated the relationship between plasma concentrations and cardiovascular effects during combined administration of diltiazem and propranolol in dogs anaesthetized with thiopental and found that the magnitude of cardiovascular depression resulting from diltiazem and propranolol in combination is dependent on the plasma concentration of both the agents. Kohno *et al*. (1977) investigated the phramacokinetics and bioavailability of diltiazem and found that the drug appeared in plasma 0.25 hour after ingestion and excreted within seven hrs, an the mean maximum plasma level was about 11 µg/100 ml at 0.5 hour. Bauer *et al*. (1986) studied the interaction of diltiazem HCl with antipyrine and indocyamine. Diltiazem HCl decreased the clearance of antipyrine but no change was observed with indocyamine. Choi and Chang (1993) studied the interaction between diltiazem HCl and phenytoin. It was seen that plasma concentration and AUC of phenytoin were increased significantly but volume of distribution and total body clearance decreased significantly. From these results, it is desirable that dosage regimen of phenytoin should be adjusted and that therapeutic drug monitoring should be practiced for reduction of side or toxic effects when phenytoin is given with diltiazem HCl in clinical practice.

The aim of the present study is to evaluate the interaction of ibuprofen and naproxen with diltiazem HCl through studying the effect of ibuprofen and naproxen on plasma concentration of diltiazem and thus to infer about the fate of combined drug therapy of these drugs.

Materials and Methods

Apparatus: An uv-vis recording spectrophotometer (UV-160, Shimadzu, Japan) was used for the measurement of absorbance of plasma samples. A centrifuge machine was used to centrifuge the blood samples to collect the plasma. Orogastric tube set was used to administer drug solution.

Chemicals: Ibuprofen, naproxen and diltiazem HCl were obtained from Beximco Pharmaceuticals Ltd. Dhaka, Bangladesh.

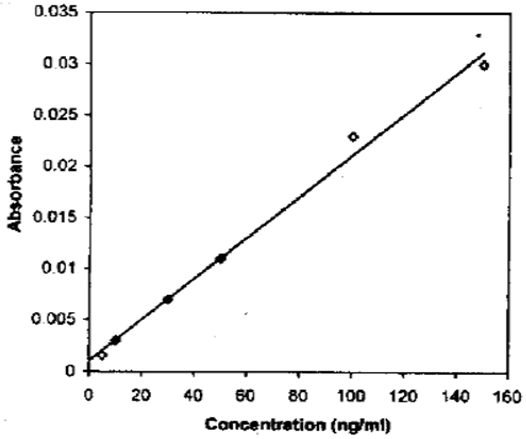

Fig. 1: Calibration curve of diltiazem HCL for analysis the *in vivo* plasma concentration by UV method

Standard solutions: Ibuprofen, naproxen and diltiazem HCl were dissolved in 10% ethanol in demineralized water separately. These stock solutions were diluted to desired strengths by buffer solution to get the working standard solution (1 µg/ml).

Test animals and administration of drug: Eighteen adult and healthy rabbits (male) were used for determination of plasma concentration. Each rabbit was of 3.0±0.2 kg body weight. Animals were collected frome the Animals Resources Branch, International Centre for Diarrheal Disease Research (ICDDR'B), Dhaka, Bangladesh. Rabbits were kept rest for seven days with normal diets. Fifteen rabbits were divided into three groups each having five (marked as I, II and III) and three as control. 3.0 mg of diltiazem HCl alone and its 1:1 mixtures with ibuprofen and naproxen were administered by orogastric tube individually in each group except control which were given the vehicle only. They were overnight fasted before drug administration. Venous blood samples (2 ml) were collected from the ear vein into heparinized centrifuge tubes before drug administration and at 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 hours after drug administration. All blood samples were protected from light, immediately centrifuged at 30900 rpm for 0 minutes and the plasma samples were separated into vials and kept into deep freeze up to analysis.

Preparation of a calibration curve: For determination of peak plasma concentration of diltiazem HCl in rabbit, the external standard method was followed. Here a six points calibration curve (Fig. 1) was obtained by plotting absorbance of the drug against its known concentration. For preparing such calibration curve, control plasma samples (1 ml) were taken with 5, 10, 30, 50, 100, 150 ng/ml diltiazem HCl. Then absorbances were measured at 240 nm.

Statistical analysis: The results were expressed as mean±s.e.m. values for each experiment.

Results and Discussion

The *in vivo* effects of ibuprofen and naproxen on plasma concentration of diltiazem HCl have been studied by observing the change in plasma concentration of diltiazem HCl in rabbit by UV spectroscopic method. Plasma concentration of diltiazem was determined after oral single administration of diltiazem HCl (3.0 mg) alone and with ibuprofen (3.0 mg of each) and also with naproxen (3.0 mg of each) in rabbits by using a calibration curve. It was found that the peak plasma concentration of diltiazem HCl is 154.6 ng/ml which was obtained after 2 hours of oral administration of diltiazem alone (Fig. 2). This peak time is within the normal range. The normal range of peak time for diltiazem is about 0.5-2.0 hours. The oral concurrent administration of diltiazem HCl and ibuprofen mixture (3.0+3.0 mg) did not make a significant change in plasma concentration of diltiazem HCl (Fig. 3). In this case the peak plasma concentration of diltiazem HCl was 159.6 ng/ml which is comparable with that obtained after administration of diltiazem HCl alone. This indicates that ibuprofen does not make any intervention in the plasma protein binding of diltiazem and thus cause hardly any change in plasma concentration of diltiazem. Hence the pharmacokinetic and thereby pharmacological or toxic effect of diltiazem may not be affected by ibuprofen with concurrent administration.

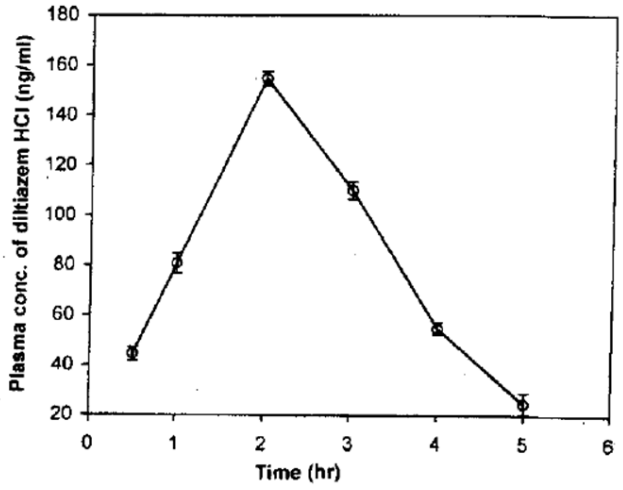

Fig. 2: Plasma concentration of diltiazem HCL when administer alone (standard deviation error bars shown)

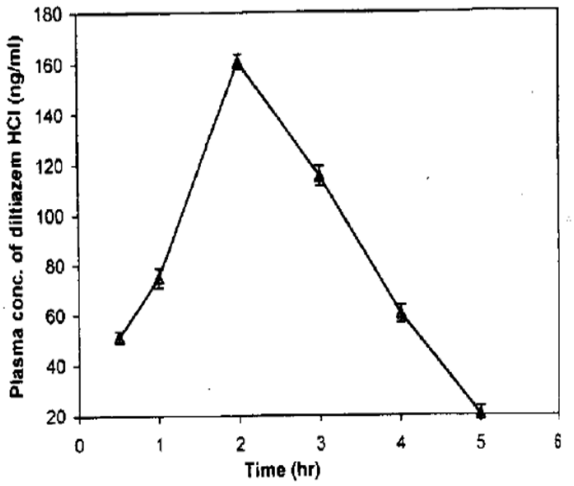

Fig. 3: Plasma concentration of diltiazem HCL after coadminister with ibuprofen (standard deviation error bars shown)

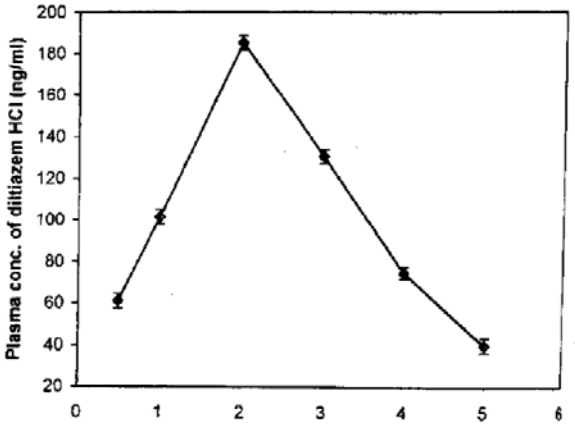

Fig.4: Plasma concentration of diltiazem HCL aftre coadminister with naproxen (standard deviation error bars shown)

The oral concurrent administration of diltiazem HCl and naproxen mixture (3.0+3.0 mg) was found to make a significant change in plasma concentration of diltiazem HCl in the same animal (Fig. 4). In this case the peak plasma concentration of diltiazem HCl was 185.25 ng/ml which is significantly greater than that obtained after administration of diltiazem HCl alone. This may be due to the higher affinity of naproxen for protein (the plasma protein binding of naproxen is >99%). So a competitive inhibition of the binding of plasma protein by naproxen increases the plasma concentration of diltiazem HCl. Such interaction of the drugs that affect the binding of plasma protein and subsequently that change the plasma concentration of drugs are very vital to be given priority in the drug therapy. Since drug displaced form plasma protein will

redistribute into its full potential volume of distribution, the concentration of free drug in plasma and tissues after redistribution may be increased only slightly (Gilman *et al.*, 1981). But this may change the pharmacokinetic properties of the drug and thereby may affect its pharmacological and toxic effects.

The *in vivo* study for determination of plasma concentration of diltiazem in rabbits by UV spectroscopic method shows that concurrent administration of diltiazem HCl and ibuprofen does not make any significant change in plasma concentration of diltiazem HCl. But administration of diltiazem in the same animal. An optimum or desired therapeutic concentration range of a drug is required where it produces its characteristic effects. Thus any change in plasma concentration may affect the pharmacological or toxic effects of the drug (Rahatuzzaman *et al.*, 1999). So care and monitoring must be practiced during combination therapy of diltiazem with ibuprofen or naproxen, particularly with naproxen to avoid any consequence of untoward incidents or harmful interactions.

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