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IN VIVO EVALUATION OF FAMOTIDINE AND PROCHLORPERAZINE MALEATE ON THE SERUM CONCENTRATION OF NIFEDIPINE IN RABBITS

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ABSTRACT

An *in vivo* study has been carried out to evaluate the influence and/or interaction of famotidine and prochlorperazine maleate on the serum concentration of nifedipine in rabbits. The study has been carried out by High Performance Liquid Chromatographic (HPLC) method. It has been found that the concurrent administration of nifedipine and famotidine has no effect on plasma concentration of nifedipine in rabbits. But concurrent administration of nifedipine and prochlorperazine maleate causes a significant decrease in plasma concentration of nifedipine. These results indicate that great care and monitoring is to be practised during concurrent administration of nifedipine with prochlorperazine to avoid untoward pharmacological and therapeutic actions related to drug-drug interactions.

INTRODUCTION

Nifedipine 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). Famotidine is an inhibitor of H_2 receptors and is used in the treatment and maintenance of active duodenal ulcers, management of pathological hypersecretory conditions such as Zollinger-Ellison syndrome and multiple endocrine adenomas (Martindale, the extra pharma-copea, 1993, Remington's Pharma-ceutical Sciences, 1990). Pro-chlorperazine maleate is an antipsychotic agent that controls the psychomotor agitation of schizophrenia, the maniac phase of maniac depressive psychosis, and the anxiety, tension & confusion associated with various neuroses (Clarke, 1986, Clayton, 1984).

Dargie *et al.* (1981) studied the interaction between nifedipine and 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 were significantly reduced by each of the active drugs and their combination added significantly to the effectiveness. Lever *et. al.* (1984) studied the influence of nifedipine on the bronchodilator effect of salbutamol in ten male asthmatic volunteers. The result suggests that nifedipine prolongs the bronchodilator action of salbutamol *in vivo*. Van Lith and Appleby (1985) studied the quinidine-nifedipine interaction. They found that the dose-related increase in quinidine serum concentrations are significantly suppressed by concurrent nifedipine therapy. Hamman *et. al.* (1987) evaluated the relationships between plasma concentrations and cardiovascular effects during combined administration of nifedipine and propranolol in dogs anaesthetised with thiopental and found that the magnitude of cardiovascular depression resulting from nifedipine and propranolol in combination is dependent on the plasma concentration of both the agents. Fraker *et. al.* (1995) examined the influence of propranolol, nifedipine or verapamil pre-treatment on the myocardial depression effect of cocaine in thirteen chronically instru-

mented, conscious dogs. Cocaine alone (4 mg/Kg I.V.) caused significant increase in heart rate (HR), mean arterial pressure (MAP), and rate pressure product (RPP). Pre-treatment with propranolol (0.5 mg/Kg I.V.) blunted the rate pressure response to cocaine by 28%. Pre-treatment with verapamil (10 mg I.V. 10 min before cocaine) blunted the rate pressure response very little. Nifedipine (90 mg sustained release orally administered 5 h earlier) also reduced the myocardial depressant effect of cocaine at 2 min. Westphal *et. al.* (1990) investigated the influence of nifedipine on the intestinal uptake of amoxycillin. They found that nifedipine significantly enhanced both absorption rate and bioavailability of amoxycillin without modifying its distribution and elimination. Busse *et. al.* (1991) studied the combined use of nifedipine and diltiazem for the treatment of severe hypertension. They showed that there is a synergistic effect on receptor binding as well as increased drug levels with the concurrent use of diltiazem and nifedipine.

The aim of the present study is to evaluate the interaction of famotidine and prochlorperazine maleate with nifedipine through studying the effect of famotidine and prochlorperazine maleate on serum concentration of nifedipine and thus to infer about the fate of combined drug therapy of these drugs.

MATERIALS AND METHODS

A. Apparatus

A High Performance Liquid Chromatographic (HPLC) machine (Simadzu, Kyoto, Japan) was used for the measurement of serum concentration of nifedipine in the rabbits, Degassing unit (Shimadzu, Kyoto, Japan), 0.45 filter paper (Millipore, Type HA, WATERS, USA), Microsyringe, Vortex mixer, centrifuge & microcentrifuge.

B. Chemicals

Famotidine was obtained from Ciba-Geigy (Presently Novartis, Bangladesh) Ltd., nifedipine was kindly supplied by ACME Laboratories Ltd., (Bangladesh) and prochlorperazine maleate was supplied by Rhone-Poulenc Rorer (Bangladesh) Ltd.

C. HPLC Method

The mobile phase

The mobile phase consisted of acetonitrile : water (48:52 % v/v) adjusted to pH 4.0 with glacial acetic acid. Each time this phase was filtered and degassed prior to use with a 0.45 filter paper. The mobile phase was pumped isocratically at a flow rate of 1.8 ml/min at ambient temperature. The effluent was monitored using UV detection at 240 nm and attenuation at 0.05 a.u.f.s.

The stationary phase

The stationary phase was a Nova Pak C-18 column.

Standard solutions

Nifedipine was dissolved in 10% ethanol in demineralized water. This stock was diluted 100 folds in HPLC grade water to get the working standard solution.

Test animals and administration of drug

Eighteen rabbits (male) were used for determination of serum concentration. Each rabbit was of 1.5 ± 0.2 Kg body weight. Animals were collected from the Animal Resources Branch, 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. 0.5 mg nifedipine alone and its 1:1 mixtures with famotidine and prochlorperazine maleate were administered by orogastric tube individually in each group. 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, 5.0 and 6.0 hours after drug administration. All blood samples were protected from light, immediately centrifuged at 3000 rpm for 10 min and the plasma samples were separated into vials and kept into deep freeze up to analysis.

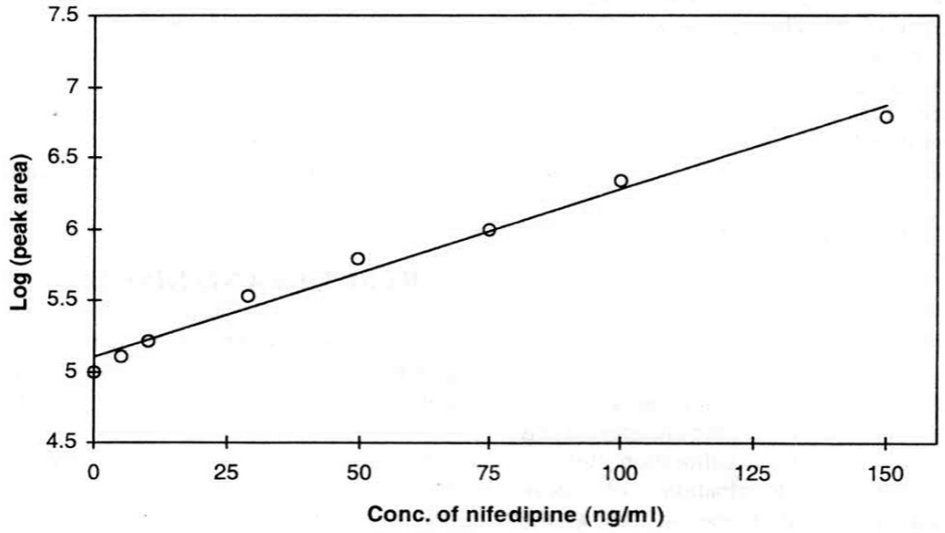


Fig. 1: Calibration curve of nifedipine for analysis by HPLC.

D. Analytical procedure

1 ml of plasma sample, 50µl of 20% sodium metabisulphite and 500 of 1M sodium bicarbonate were taken in screw-capped glass centrifuge tube (10 ml). The mixture was shaken on a vortex mixer for 30 s. For extraction, 5 ml of diethylether were added and the mixture was shaken on a vortex mixer for 1 min and centrifuged for 10 min at 3000 rpm. After centrifugation, the organic layer

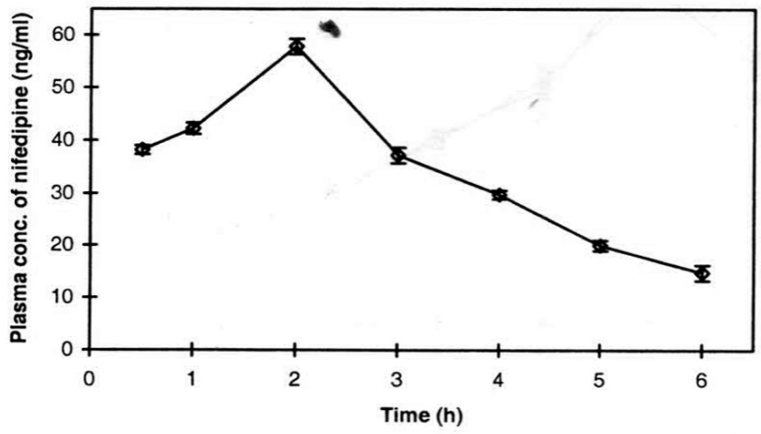


Fig.2: Plasma concentration of nifedipine after administration of nifedipine alone (standard deviation error bars shown).

was transferred into another glass centrifuge and evaporated to dryness under a stream of nitrogen at 45 °C. The residue was dissolved in 250 the mobile phase, vortexed for 30 s and transferred to a disposable polypropylene microcentrifuge tube (1.5 ml Eppendorf tube) and centrifuged for 2 min at 11500 rpm in a microcentrifuge to ensure that no particulate matter would be injected into the column. An appropriate aliquot of 25-40 was then injected directly in to the loop injector (El-Sayed 1993). The chromatograms obtained from test samples were quantified by using a calibration curve.

E. Preparation of a calibration curve

For quantification of the chromatograms obtained from HPLC, a calibration curve is required. For determination of peak concentration of nifedipine in rabbit, the external standard method was followed. Here a eight points calibration curve (Figure 1) was obtained by plotting log (peak area) of the drug against its known concentration. For preparing such calibration curve, control plasma samples (1 ml) were taken with 0, 5, 10, 25, 50, 75, 100 and 150 ng/ml nifedipine. Standard samples were processed identically and simultaneously as described (Westphal 1990).

F. Statistical analysis

The results were expressed as mean ± s.d. values for each experiment.

RESULTS AND DISCUSSION

The *in vivo* effects of famotidine and prochlorperazine maleate on plasma concentration of nifedipine have been studied by observing the change in plasma concentration of nifedipine in rabbit by HPLC method. Plasma concentration of nifedipine was determined after oral single administration of nifedipine (0.5 mg) alone and with famotidine (0.5 mg of each) and also with prochlorperazine maleate (0.5 mg of each) in rabbits.

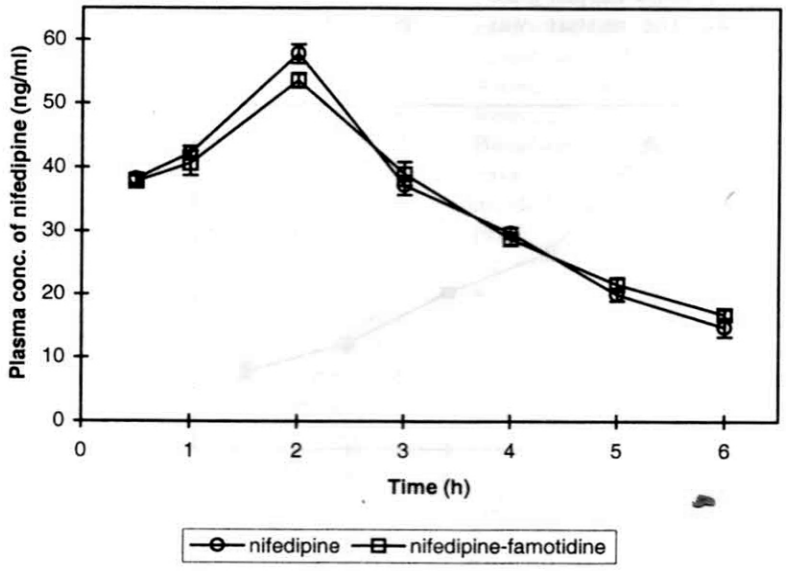
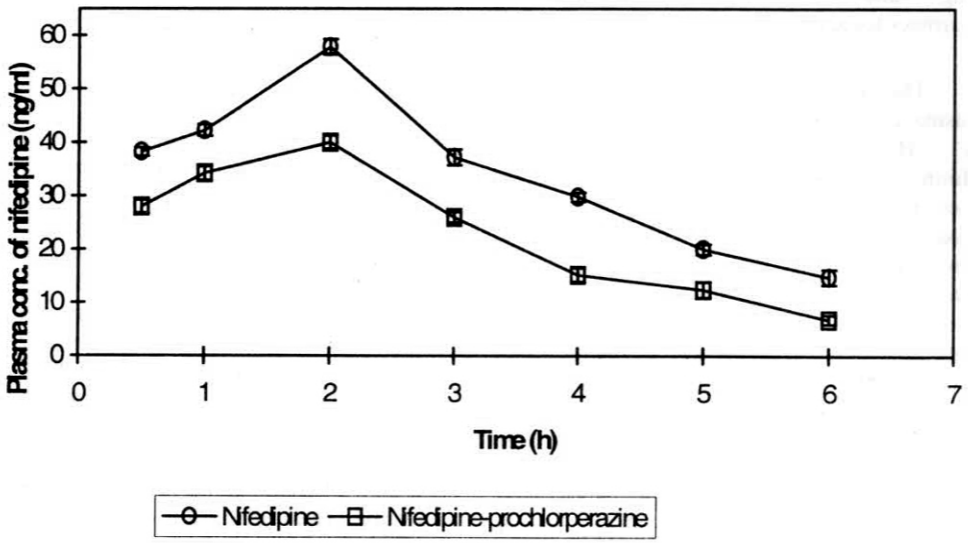


Fig. 3: Plasma concentration of nifedipine after administration of nifedipine with famotidine (standard deviation error bars shown).

Fig. 4: Plasma concentration of nifedipine after administration of nifedipine with prochlorperazine (standard deviation error has bars shown).



It was found that the peak plasma concentration of nifedipine is 57.8 ng/ml which was obtained after 2 h of oral administration of nifedipine alone (Figure 2). This peak time is within the normal range. The normal range of peak time for nifedipine is about 0.5-2.0 h. The oral concurrent administration of nifedipine and famotidine mixture (0.5 mg + 0.5 mg) did not make a significant change in plasma concentration of nifedipine (Figure 3). In this case the peak plasma concentration nifedipine was 53.6 ng/ml which is comparable with that obtained after administration of nifedipine alone. This may be due to lower affinity of famotidine for plasma because the plasma protein binding of famotidine is about 05-15% and that of nifedipine is about 92-98%(Clayton 1984, Martindale the extrapharmacopea 1993) or may be due to negative effect of famotidine on gastrointestinal (GI) absorption of nifedipine as it is rapidly and almost completely absorbed following oral administration (Clayton 1984, Martindale the extrapharmacopea 1993). Hence the pharmacokinetic and thereby pharmacological or toxic effect of nifedipine may not be affected by famotidine with concurrent administration.

The oral concurrent administration of nifedipine and prochlorperazine maleate mixture (0.5 mg + 0.5 mg) was found to make a significant change in plasma concentration of nifedipine in the same animal (Figure 4). In this case the peak plasma concentration of nifedipine was 40 ng/ml which is significantly less than that obtained after administration of nifedipine alone. This may be due to the interaction leading to formation of complex of nifedipine with prochlorperazine maleate (Akhter 1996). This results in the low plasma concentration of nifedipine when administered with prochlorperazine maleate.

Such interaction can displace the drug from blood plasma. Since drug displaced from plasma protein will redistribute into its full potential volume of distribution, the

concentration of free drug in plasma and tissue after redistribution may be increased only slightly (Gilman, 1991). 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 nifedipine in rabbits by HPLC shows that concurrent administration of nifedipine and famotidine does not make any significant change in plasma concentration of nifedipine. But administration of nifedipine and prochloperazine maleate causes a significant alteration if plasma concentration of nifedipine 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 (Rahat et al., 1999, Bari et al, 2000). So care and monitoring must be practised during combination therapy of nifedipine with famotidine or prochlorperazine maleate, particularly with prochlorperazine maleate to avoid any consequence of untoward incidents or harmful interactions.

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