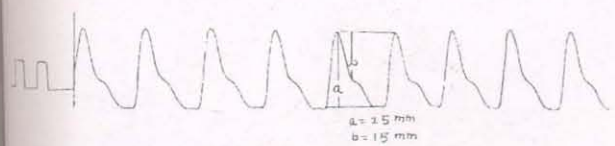
organic nitrates is assessed by their drug effect instead of estimation of their plasma concentrations (4). Digital pulse plethysmography (DPG) has been suggested to be the most sensitive method for the evaluation of nitrate effects (5,6). The action of nitrates on DPG is characterised by downward displacement of descending limb of the pulse curve and the dicrotle notch.

Quantifying the morphological changes observed with reference to the quotient of b/a ratio (a) height of systolic peak : (b) height of the dicrotic wave affords a simple and reliable method for assessing the action of nitrates and hence its bioavailability (7) – (Fig I). Hence, we have undertaken the present study to evaluate the bioequivalence of two formulations of ISMN, by DPG.



Representative tracing of Digital pulse plethysmogram showing systolic peak "a" and dicrotic Incisura "b"

Fig. I

Material and Methods

Twenty four healthy male volunteers with normal cardiovascular, renal, hepatic, haematological and biochemical parameters participated in this randomized, double blind crossover study conducted at the Department of Clinical Pharmacology and Therapeutics at Nizam's Institute of Medical Sciences, Hyderabad. The study had been approved by the Institutional Ethical Committee. Each volunteer had given his written informed consent for participation in this study.

All the volunteers who were smokers, hypotensives, had a history of drug allergy, or had no evidence of dicrotic notch in the DPG were excluded from the study. The volunteers were housed in the Department of Clinical Pharmacology and Therapeutics on the previous night of the study and were not allowed to take any food after 10 P. M. On the next morning, before commencement of the study blood pressure (B.P.) along with the heart rate (H.R.) were recorded using (L&T Minimon 7133 A) B.P. monitor and the pulse wave curve was recorded by a photo electric transducer (L&T Micromon 7142) fixed to the distal phalynx of the right index finger. The magnified signals of the pulse curve were then recorded on ECG recorder (BPL Cardiart 1087) at a chart speed of 25 mm/sec. The b/a ratio was calculated by dividing the height of dicrotic notch (b) by the height of the systolic peak (a) from the mean of three consecutive digital pulse curves.

Volunteers were given one tablet of formulation A - standard (Isosorbide 5 mononitrate : IMDUR 60 mg ER tablet ; KEY Pharmaceuticals) or formulation B - test (Isosorbide 5 mononitrate : IMNIT 60 mg SR tablet ; Dr. Reddy's Laboratories, Hyderabad) as per a randomization schedule on a empty stomach with 150 ml of water. The volunteers were crossed over to the next formulation after a washout period of two weeks.

The recording of the pharmacodynamic parameters such as B.P., H.R. and pulse wave curve were again carried out in a quiet room at constant temperature in supine position on the bed at an interval of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, and 24 hours after the administration of the ISMN formulations. Standard breakfast and lunch were provided ater 3.0 and 6.0 hours after the drug administration. Caffiene containing beverages were not allowed throughout the study period. Occurrence of any side effects were recorded in the case record form. If

any volunteer complained of headache during the study period he was given 500 mg of tablet paracetamol.

Pharmacodynamic Parameters Evaluated

1. E max - Maximum (peak) effect observed in b/a ratio.
2. T max - Time to reach maximum (peak) effect.
3. AUC 0-24 hrs - Area under the effect time curve from 0-24 hrs.

Statistical Evaluation

The pharmacodynamic variables were compared by paired 't' test.

Results

Twenty-four healthy male volunteers with mean age of 25.33 ± 2.46 years, mean height of 167 ± 6.0 cms and mean weight of 63 ± 8.0 kg participated in the study. The basal values of the pharmacodynamic variables like b/a ratio, B.P. and H.R. were comparable between the two treatment groups. Administration of both the ISMN formulations produced downward displacement of the dicrotic notch in the descending limb of the pulse curve producing an increase in the b/a ratio at different time intervals as compared to the base line.

Both the standard as well as the test formulations increased the b/a ratio within half an hour after the administration of the drug and this was maintained till the end of 20 hours. The effect of ISMN on b/a ratio and the mean percentage change in b/a ratio from the baseline at various time intervals is shown in Fig. II and III respectively. Individual pharmacodynamic parameters like peak effect (Emax), time to obtain peak effect (tmax) and the area under the effect - time curve (AUC 0-24 hrs) obtained with the two formulations are shown in Table I. There were no significant differences between these parameters after the administration of the two formulations.

An equal incidence of mild to moderate headache was reported by the volunteers in both the treatment groups which was relieved after administration of the paracetamol tablet.

EFFECT OF ISOSORBIDDE MONONITRATE ON b/a RATIO

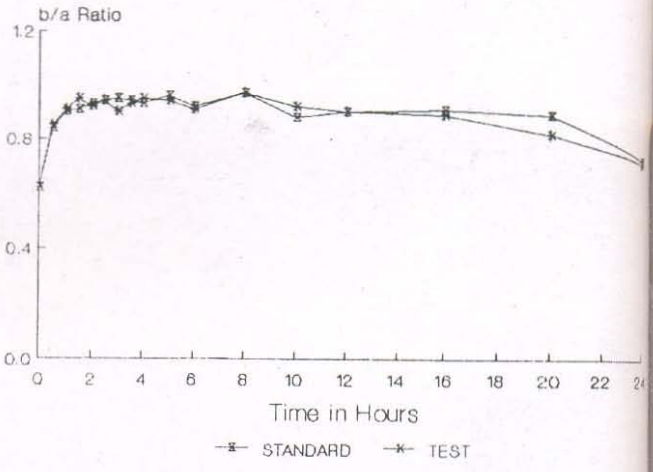


Fig. II

EFFECT OF ISOSORBIDDE MONONITRATE ON % CHANGE IN b/a RATIO

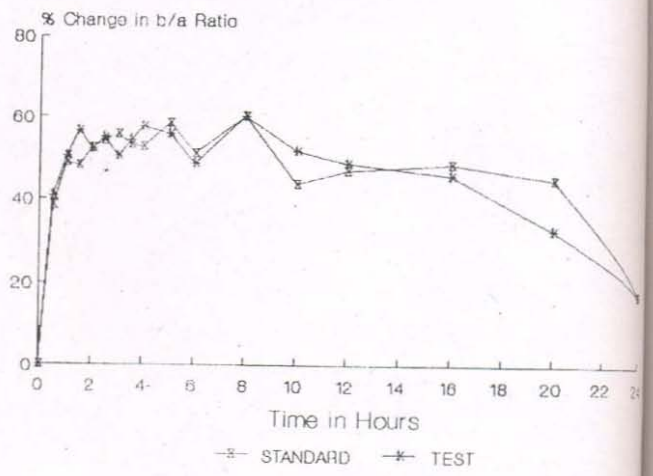


Fig. III

TABLE I

PHARMACODYNAMIC PARAMETERS

	STANDARD			TEST		
Vol.	Emax b/a Ratio	tmax hr.	AUC b/a Ratio/hr.	Emax b/a Ratio	tmax hr.	AUC b/a Ratio/hr.
1.	0.88	3.5	19.40	0.96	10.0	21.69
2.	0.93	8.0	16.90	0.77	3.5	15.56
3.	1.00	1.0	20.81	1.00	6.0	21.71
4.	1.08	2.0	23.00	1.00	1.0	22.77
5.	1.10	3.0	20.30	1.05	1.5	21.00
6.	0.93	2.0	21.64	1.00	2.5	21.08
7.	1.09	2.0	23.35	1.04	8.0	21.80
8.	1.06	5.0	21.85	1.05	2.0	22.16
9.	1.08	6.0	22.23	1.17	8.0	23.18
10.	1.08	8.00	23.95	1.13	2.5	24.35
11.	1.14	2.00	23.14	1.08	4.0	22.66
12.	0.92	2.6	20.17	1.00	2.5	21.62
13.	1.00	1.0	21.10	0.94	5.0	18.72
14.	1.00	0.5	22.63	1.13	4.0	22.60
15.	1.05	4.0	22.14	1.00	1.5	19.09
16.	1.06	5.0	21.31	1.09	4.0	20.63
17.	1.07	1.0	22.29	1.15	1.0	19.82
18.	1.10	3.0	22.64	1.11	1.0	22.23
19.	1.00	5.0	18.75	1.00	4.0	19.20
20.	1.00	2.5	19.87	0.90	8.0	17.73
21.	1.00	2.5	22.34	1.08	8.0	21.35
22.	1.01	2.5	20.76	1.08	1.0	23.00
23.	1.00	8.0	20.44	1.06	8.0	22.39
24.	1.09	2.0	22.83	1.06	2.0	20.13
MEAN	1.03	3.38	21.41	1.04	4.08	21.09
S.D.	0.07	2.22	1.65	0.09	2.81	1.97

Discussion

Although most bioequivalent studies are based on plasma concentration time profile curve a pharmacodynamic approach is found to be most appropriate with nitrates because it is difficult to estimate nitrates in biological fluids due to their very low concentrations and significant loss in vitro (8).

The pharmacological response of a drug in healthy volunteers is clinically related to the effect of the drug in patients (9) as seen with the prolongation of PQ interval with diltiazem which is observed both in healthy volunteers as well as in patients. This is clinically related to the anti-arrhythemic effect of diltiazem (10). Similarly the pharmacological response of ISMN was quantifiable with reference to b/a ratio obtained from the DPG.

Bio-availability of nitrates can be measured by different methods like measuring left ventricular or artierial as well as pulmonary circulation pressure and also by measuring cardiac output. In this study we had undertaken to compare the bioequivalence of two formulations of ISMN by using DPG because it had

proved to be a simple, non-invasive, sensitive and informative technique for studying the effects of the nitrates. On the basis of observations in the DPG some indirect conclusions of the coronary arteries are also jusitied (11).

Administration of both the ISMN formulations produced characteristic downward displacement of the dicrotic notch in the descending limb of the pulse curve producing an increase in b/a ratio at different time intervals as compared to the baseline. There was no statistical significance in the values of Emax, tmax and AUC 0-24 hours.

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ORIGINAL ARTICLE

Bioequivalence Study of two Long Acting Isosorbide Mononitrate Formulations Assessed by Digital Pulse Plethysmography

Mohsin Mohd*, M.U.R. Naidu*, Jaydip Bhadun**, Aravinda Babu P**, T. Ramesh Kumar Rao*

Abstract

Twenty-four healthy human volunteers were randomized to receive 60 mg of Isosorbide 5 mononitrate of either formulation A or B in a double blind, cross over study. The vasodilatory response (b/a) ratio of pulse curve was recorded by digital pulse plethysmography at various time intervals over a period of 24 hours. A wash out period of 2 weeks was given before the administration of the next formulation. Both the standard as well as the test formulations increased the b/a ratio within half an hour after the administration of the drug and this was maintained till the end of 20 hours. The E max, t max and AUC 0-24 hours were 1.03 ± 0.07, 3.38 ± 2.22 hours and 21.41 ± 1.65 b/a ratio / hr for the standard formulation and 1.04 ± 0.09, 4.08 ± 2.81 hours and 21.09 ± 1.97 b/a ratio / hr for the test formulation. There was no significant differences between these parameters after the administration of the two formulations. Both the formulations were well tolerated.

Key Words

Isosorbide mononitrate, Digital pulse plethysmography, Bioequivalence.

Introduction

Nitrates are among the most widely used antianginal drugs (1). The antianginal efficacy of nitrates is the result of haemodynamic changes, like dilatation of veins, arteries, arterioles and the coronary vessels. The vasodilating effect of nitrates increases linearly with increasing plasma concentrations(2). The pharmacokinetic profile of Isosorbide 5 mononitrate (ISMN) is less complicated than glyceryl trinitra and isosorbide dinitrate. ISMN does not underg first pass extraction by the liver and is most oft used for long term therapy for angina pectoris (There is a close correlation between serum dr levels and haemodynamic parameters obtain following acute administration. The bioavailability

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