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Research Article

EFFECT OF FOOD ON THE ABSORPTION OF METFORMIN FROM SUSTAINED RELEASE METFORMIN HYDROCHLORIDE FORMULATIONS IN HEALTHY INDIAN VOLUNTEERS

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ABSTRACT

Objectives: Sustained release (SR) metformin hydrochloride formulations are usually administered with meals, which can result in dose dumping, which in turn can affect their safety profile. We examined the effect of co-administration of food on the bioavailability of metformin from SR formulations in healthy Indian volunteers.Methods: In an open-label, three-period, six-sequence crossover study, 30 healthy males, aged 18 to 43 (mean 29) years were randomly assigned to a single tablet of treatment A (metformin hydrochloride SR 1000mg, fasted condition), B (metformin hydrochloride SR 1000mg, fed state) or C (metformin hydrochloride SR 1000mg/glimepiride 2mg, fed state) with a one week washout between treatments. Plasma concentrations of metformin were measured using LC-MS/MS. Log-transformed AUC and C_{max} fed: fasted ratios were used to determine bioavailability. Tolerability was assessed using physical examination and laboratory analysis.Results: Pharmacokinetic analysis was performed on the first 24/25 volunteers who completed the study. Following a high fat meal, C_{max} from treatments B and C increased by nine and seven percent; AUC increased by 17% and seven percent respectively compared to treatment A. Seven mild adverse events were reported in six participants.Conclusions: Food slightly increased the bioavailability of metformin from metformin hydrochloride 1000mg SR tablet and from a fixed dose combination of metformin hydrochloride 1000mg SR/glimepiride 2mg, with no evidence of dose-dumping of metformin from either formulation. The treatments were well tolerated.

Keywords: sustained release, metformin hydrochloride, food, dose dumping, bioavailability, healthy, Indian

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in India is projected to increase from 31.7 million cases in 2000 up to 79.4 million by 2030.[1] Given as a single dose with food, sustained release (SR) formulations of metformin hydrochloride offer the convenience of once daily administration. However, the potential for dose dumping when co-administered with food can result in potential safety risk for patients due to a rapid increase in plasma metformin levels. [2, 3, 4] This study examined the magnitude of food effect on the bioavailability of metformin from metformin hydrochloride SR and metformin hydrochloride SR/glimepiride formulations.

MATERIALS AND METHODS

Objectives

The primary objective of this study was to compare the bioavailability of metformin given in a fed condition either as metformin hydrochloride 1000mg SR tablet (Metlead ™ Forte SR, Treatement B) or as a fixed dose combination (FDC) of metformin hydrochloride 1000mg SR/glimepiride 2mg tablet (Metlead ™ G2 Forte, Treatment C) with that given in fasting condition as metformin hydrochloride 1000mg SR tablet (Metlead ™ Forte SR, Treatment A) in healthy Indian volunteers. We also assessed the tolerability of the treatment regimens.

Clinical study design

This was a randomized, single dose, single center, open-label, 3-period, 6-sequence, crossover study in 30 healthy adult Indian males. Participants were randomly assigned in equal numbers to 6 sequences of treatment regimens A (metformin hydrochloride SR 1000mg tablet in fasted state), B (metformin hydrochloride SR 1000mg tablet in fed state) and C (FDC, metformin hydrochloride SR 1000mg/glimepiride 2mg tablet in fed state) (Figure 1).

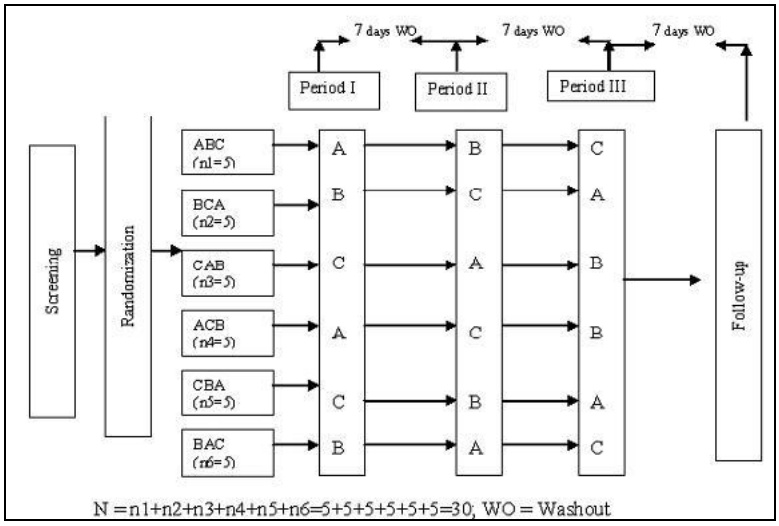

Figure 1: It Shows Assignment To Treatments

In the fasted state, participants received the study medication at approximately 8:00 hours after a 10-hour overnight fast. In the fed state, participants were allowed approximately 15 minutes to consume an entire standard high-fat breakfast consisting of slices of

bread with 20gm of butter (60g), chicken pieces (75 gm), eggs (20 gm), hash brown potatoes with five gm butter (90gm) and whole milk (240 ml) to provide 960 kcal (54% of calories from fat, 20% from protein and the rest from carbohydrates). Participants received study medication at 8:00 hours. All treatments were taken orally with 240 ml of a 20% glucose solution followed by 60ml of the glucose solution administered every 15 minutes for up to four hours after dosing to reduce the risk of hypoglycemia. Mouth and hand checks were done to ensure that every participant swallowed the study medication. A seven-day washout separated the dosing regimens assigned to each participant. In the fasted state, food was prohibited for four hours following ingestion of study medication. Breakfast, lunch and dinner were served at four, eight and 13 hours post dosing respectively. In the fed state, lunch, snacks and dinner were served at four, nine and 13 hours post dosing respectively.

The study was conducted at the clinical research unit of a Clinical Research Organisation. The study protocol was reviewed and approved by an Independent Ethics Committee.

Participants

A sample size of 24 participants was chosen based upon previous literature reports of similar studies.[5] Considering a potential dropout rate of 20%, a total of 30 volunteers were enrolled into the study. Written informed consent was obtained from all participants prior to enrolment. Participants were considered eligible for enrolment based upon inclusion/exclusion criteria for healthy male volunteers.

Blood sampling

Blood samples for measurement of plasma metformin concentrations were mostly collected through an intravenous cannula; direct venipuncture was used for the last 3 samples. Blood was collected in vacutainers containing six ml K_3EDTA (Di-Potassium Ethylene Diamine Tetra Acetic Acid). Sufficient blood (six ml) was collected to provide approximately two ml plasma from each sample. Blood samples were collected within one hour prior to dosing (zero hour) and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24 and 30 hours after dosing in each treatment period and were centrifuged within 30 minutes of collection to separate the plasma. Plasma samples were frozen within two hours after collection and maintained at -16^{0}C or colder.

Bioanalytical method

A total of 1296 plasma samples were collected and analysed in this study. Plasma concentrations of metformin were determined using a validated LC-MS/MS system with carbamazepine as internal standard at Vimta Labs Ltd. The lower calibration curve concentration was 15.05 ng/ml.

Pharmacokinetic analysis

The plasma pharmacokinetic (PK) parameters of metformin were calculated using non-compartmental analysis with Phoenix ™ WinNonlin Professional software (Version 6.1, Pharsight Corporation, USA). The pharmacokinetic parameters included the area under the plasma concentration-time curve (AUC) from time zero to time of the last measurable concentration (AUC_{0-t}), the AUC from time zero to infinite time ($AUC_{0-\infty}$), the ratio AUC_{0-t}/ $AUC_{0-\infty}$, the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), elimination constant (k_{el}), terminal phase elimination half life ($t_{1/2}$) and pharmacokinetic lag time (T_{lag}). The pharmacokinetic analysis was performed on the samples obtained from the first 24 completed study participants.

Statistical analysis

Statistical analyses were performed using SAS® Enterprise Guide 4.2 (Version 9.2, SAS Institute Inc. Cary, NC, USA). Summary statistics (N, arithmetic mean, SD, 95% CI for the arithmetic mean, median, geometric mean, minimum, maximum, % CV) were calculated for all the PK parameters for each of the treatments A, B and C. To compare the bioavailability of metformin from fed vs. fasted states (B/A and C/A), the log-transformed individual C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were compared using a mixed–model ANOVA with sequence, period and treatment regimen as fixed effects. The mean differences were back transformed to obtain geometric mean of test/reference ratios (GMRs) and their 90% CI.

Safety assessments

Safety was assessed by monitoring vital signs, ECG and clinical laboratory tests at pre-specified time points during the study. Adverse events were obtained by monitoring and questioning participants.

RESULTS

Demographics

25/30 participants completed the study (Fig. 2). The average age of the subjects was 28.8 years (SD 6.6). Their average weight and height was 65.6 kg (SD 3.8) and 166.5 cm (SD 4.6) respectively with a mean BMI of 23.7 kg/m^2 (SD 1.2).

Pharmacokinetic parameters

The mean plasma concentration-time profiles of metformin for treatment regimens A, B and C are shown in Figure 3. There were no statistically significant sequence or period effects for C_{max} and AUC of metformin.

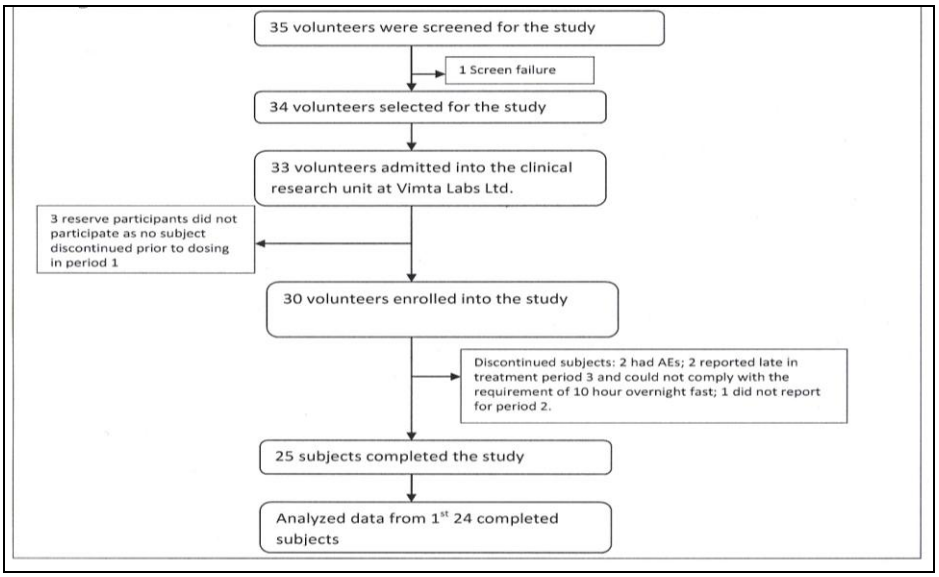

Figure 2: It Shows The Flow Chart Of Subjects

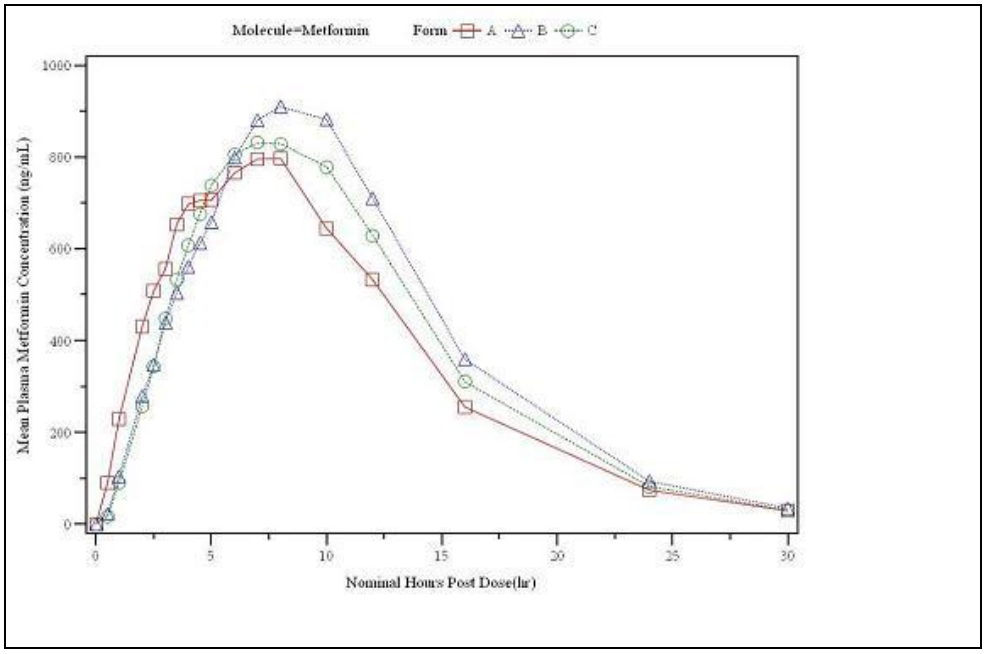

Figure 3: it shows the mean plasma metformin concentration-time profiles in healthy males (n=24) after a single dose of metformin SR 1000mg tablet in fasted state (A) and in fed state (B) and metformin hydrochloride SR 1000mg/glimepiride 2mg tablet in fed state (C)

The mean C_{max} of metformin with A, B and C were 915.98 ng/ml, 994.82 ng/ml and 975.77 ng/ml respectively; mean $AUC_{0-\infty}$ was 10602.92 ng.hr/ml, 12073.31 ng.hr/ml and 11164.76 ng.hr/ml respectively; median T_{max} was eight hours for each treatment; mean $t_{1/2}$ was 4.58 hours, 4.12 hours and 4.22 hours respectively (Table 1).

Table 1: shows the pharmacokinetic parameters of metformin in healthy males (n=24) after a single dose of metformin SR 1000mg tablet in fasted state (A), metformin SR 1000mg tablet in fed State (B) and metformin hydrochloride SR 1000mg/glimepiride 2mg tablet in fed state (C).

Summary Statistics	Metformin (N=24)							
	C_{max} (ng/ml)	AUC_{0-t} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	T_{lag} (Hour)	T_{max} (Hour)	$t_{1/2}$ (Hour)	K_{el} (1/hr)	AUC Ratio (ng.hr/ml)
Treatment A								
Mean* (SD), 95% CI	915.98 (257.41), 807.29, 1024.68	10396.38 (3169.10), 9058.18, 11734.57	10602.92 (3213.25), 9246.09, 11959.76	0	7.15 (2.51), 6.09, 8.21	4.58 (0.98), 4.17, 5.00	0.16 (0.03), 0.15, 0.17	97.98 (0.86), 97.61, 98.34
Median	853.12	10794.07	10959.26	0	8.00	4.28	0.16	98.26
GM	884.30	9894.58	10099.26	-	-	4.50	0.15	97.97
Min, Max	554.08, 1507.29	4801.56, 17240.31	4928.84, 17546.54	0	1.00, 12.00	3.60, 7.92	0.09, 0.19	96.14, 99.14
%CV	28.10	30.48	30.31	-	35.11	21.39	16.61	0.88
Treatment B								
Mean* (SD), 95% CI	994.82 (259.98), 885.04, 1104.60	11867.17 (2968.78), 10613.57, 13120.78	12073.31 (3016.92), 10799.37, 13347.24	0.19 (0.25), 0.08, 0.29	8.27 (1.80), 7.51, 9.03	4.12 (0.45), 3.93, 4.31	0.17 (0.02), 0.16, 0.18	98.29 (0.60), 98.04, 98.54
Median	928.42	10713.64	10883.28	0	8.00	4.16	0.17	98.44
GM	963.38	11563.59	11765.20	-	-	4.09	0.17	98.29
Min, Max	572.83, 1601.14	8690.14, 19189.47	8792.25, 19679.24	0, 0.52	4.50, 12.00	3.32, 4.80	0.14, 0.21	97.10, 99.14
%CV	26.13	25.02	24.99	131.89	21.77	10.95	11.25	0.61
Treatment C								
Mean* (SD), 95% CI	975.77 (264.98), 863.88, 1087.66	10955.36 (3272.53), 9573.49, 12337.23	11164.76 (3322.61), 9761.74, 12567.78	0.27 (0.26), 0.16, 0.38	8.35 (2.41), 7.34, 9.37	4.22 (0.43), 4.03, 4.40	0.17 (0.02), 0.16, 0.17	98.09 (0.48), 97.89, 98.30
Median	935.68	10198.64	10445.04	0.50	8.00	4.20	0.17	98.20
GM	942.65	10546.91	10751.90	-	-	4.20	0.17	98.09
Min, Max	582.22, 1673.47	6407.73, 20461.00	6594.58, 20808.07	0, 0.52	4.50, 12.00	3.61, 5.15	0.14, 0.19	97.17, 98.90
%CV	27.16	29.87	29.76	93.98	28.81	10.30	9.83	0.49

*Arithmetic Mean

Effect of food on pharmacokinetics of metformin

GMRs (90% CI) of B vs. A for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 108.94 (101.01,117.50), 116.87 (107.07, 127.57) and 116.50 (106.91, 126.95) respectively. The C_{max} and AUC of metformin with treatment B increased by nine percent and 17% respectively compared to treatment A (Table 2).

The GMRs (90% CI) of C vs. A for Cmax, AUC_{0-t} and $AUC_{0-\infty}$ were 107.24 (99.37, 115.73), 107.38 (98.30, 117.29) and 107.24 (98.35, 116.94) respectively. The C_{max} and AUC of metformin with treatment C increased by seven percent each compared to treatment A (Table 3). These increases were not accompanied by an increase in Tmax.

Table 2:Shows the relative bioavailability of metformin in healthy males (n=24) after a single dose of metformin SR 1000mg tablet in fasted state (A) vs. Metformin SR 1000mg tablet in fed state (B).

PK Parameter	Least Squares Geometric Means of Treatment		Comparison	Ratio (%)	90% CI of Ratio
	Test (B)	Reference (A)			
C_{max} (ng/ml)	975.05	895.01	B vs. A	108.94	(101.01,117.50)
AUC_{0-t} (ng.hr/ml)	11609.50	9933.86	B vs. A	116.87	(107.07, 127.57)
$AUC_{0-\infty}$ (ng.hr/ml)	11808.69	10136.61	B vs. A	116.50	(106.91, 126.95)

Table 3: shows the relative bioavailability of metformin in healthy males (n=24) after a single dose of metformin SR 1000mg tablet in fasted state (a) vs. Metformin hydrochloride SR 1000mg/glimepiride 2mg tablet in fed state (C).

PK Parameter	Least Squares Geometric Means of Treatment		Comparison	Ratio (%)	90% CI of Ratio
	Test (C)	Reference (A)			
C_{max} (ng/ml)	959.77	895.01	C vs. A	107.24	(99.37, 115.73)
AUC_{0-t} (ng.hr/ml)	10666.50	9933.86	C vs. A	107.38	(98.30, 117.29)
$AUC_{0-\infty}$ (ng.hr/ml)	10870.76	10136.61	C vs. A	107.24	(98.35, 116.94)

Safety

No serious adverse events occurred during the study. A total of six subjects had seven adverse events. One subject each (1/30 or 3.3%) had fever in the pre-study period, had upper abdominal pain (within 24 hours after dosing with Treatment C, 'possibly related'), had loose motions (a day after dosing with Treatment B, 'possibly related') and one (1/30 or 3.3%) had both enzymes elevated, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (seven days after dosing with Treatment B, 'possibly related'). Two subjects (2/30 or 6.6%) had raised ALP (a day after dosing with Treatment C and B, but 'unlikely related' to study drugs). Fever was treated with paracetamol, upper abdominal pain was treated with ranitidine, loose motions were treated with a combination of norfloxacin + tinidazole and a lactic acid preparation. All adverse events were mild and resolved with no sequelae. There were no hypoglycemic events reported in this study.

DISCUSSION

There was no evidence of dose dumping when a single tablet of Metlead™ Forte SR (1000mg) or a single tablet of Metlead™ G2 Forte (1000mg/2mg) was administered to healthy male volunteers with food. Metlead™ Forte SR 1000mg was well tolerated with or without food; Metlead™ G2 Forte (1000mg/2mg) was also well tolerated when administered with food.

Metformin is primarily absorbed from the upper gastrointestinal tract. It is always administered with food to reduce gastrointestinal disturbances.[6] In addition, food prolongs the gastric retention time of sustained release metformin formulations, allowing metformin to be released in the upper gastrointestinal tract over a longer period of time compared with immediate release formulations.[7]

A pharmacoscintigraphy study of metformin-ER 500 mg tablet in 13 healthy volunteers reported an increase in bioavailability after a high fat meal ($AUC_{0-\infty}$ 6457 ng. h/ml) compared to a low fat meal ($AUC_{0-\infty}$ 4983 ng. h/ml).[7] A randomized, single dose (2x 500mg tablets of sustained release metformin hydrochloride), crossover study in 24 healthy volunteers also reported a significant increase in $AUC_{0-\infty}$ (13206 ng. h/ml) of metformin (2 x 500mg tablets) after a high fat meal compared to the fasted state (7506 ng. h/ml) corresponding to a 76% increase in systemic exposure to metformin. The high fat meal prolonged Tmax (Tmax 6.3 h) by approximately three hours as compared to the fasted state (Tmax 3.2 h) but C_{max} was not affected in fasted (C_{max} 1022 ng/ml) vs. fed (C_{max} 1018 ng/ml) conditions.[7] In yet another healthy volunteer study, following a single oral administration of 1000mg of sustained release metformin in the fed state, a mean peak plasma concentration of 1214 ng/ml was achieved with a median time of 5 hours, AUC_{0-t} was 11649 ng h/ml and $AUC_{0-\infty}$ was 11785 ng h/ml. Food increased $AUC_{0-\infty}$ by 77% and C_{max} by 26% and prolonged Tmax by 25% as compared to the fasted state.[8]

In our study, lack of intra or inter subject variability is indicated by the absence of any significant sequence or period effect. We observed a seven to nine percent rise in C_{max} and a seven to 17% rise in AUC of metformin after a high fat meal compared to the fasted state. This increase was lesser than that reported in previous studies. In contrast to earlier reports, we did not observe any prolongation in T_{max} after food.

Dose dumping refers to a rapid unintended release of a large amount of drug from a modified dosage form that can create a potential safety risk for patients.[9] This phenomenon is clinically relevant when such formulations are administered with food. The mechanical stress of the grinding action of the stomach in the fed state could introduce variability if an sustained release tablet containing metformin hydrochloride is broken down more rapidly than anticipated. Because food prolongs the gastric retention time, sustained release formulations administered with food are exposed to longer duration of mechanical stress in the stomach.[10] The latter raises the possibility of increased release rate of the drug (than intended) from the formulation. Dose dumping is usually indicated by a 50% or higher unexpected increase in C_{max} in fed vs. fasted states within two hours of administration of a drug.[11] We did not observe any such rise in C_{max} in our study. Therefore there was no evidence of dose dumping of metformin after food administration.

As expected, the most frequently (six/seven) reported adverse events were gastrointestinal in nature.[10] There were four adverse events (abdominal pain, diarrhea, raised AST and ALT) that were considered 'possibly related' to treatment. Elevated AST and ALT were detected in one subject, seven days after receipt of treatment B but there were no symptoms suggestive of hepatic dysfunction. All these adverse events are known adverse events associated with metformin. Abdominal pain and diarrhea are commonly reported with metformin therapy [12] and minor enzyme elevations (after one to eight weeks) have also been reported during metformin therapy in less than one percent of patients.[13] All adverse events resolved without any sequelae.

The C_{max} of metformin from a single dose of Metlead™ Forte SR (1000mg) and from a single dose of Metlead™ G2 Forte (1000mg/2mg) was increased by nine percent and seven percent respectively when dosed with food relative to the fasted state; AUC increased by 17% and seven percent respectively. The magnitude of the increase was in line with that expected from the literature and

there was no evidence of dose dumping. All treatment regimens were well tolerated by healthy Indian volunteers.

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