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# Pharmacokinetics and Dose Proportionality of Extended-Release Metformin following Administration of 1000, 1500, 2000 and 2500 mg in Healthy Volunteers

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**ABSTRACT:** The pharmacokinetics and dose-exposure relationship of an extended-release formulation of metformin (ER-metformin) was investigated in a randomized, single-dose, four-period crossover study in 24 healthy male volunteers. During each study period, subjects received a randomly assigned dose containing 1000, 1500, 2000 or 2500 mg metformin. Blood samples were drawn 0–72 h after dosing for pharmacokinetic and dose-proportionality assessment. Although several pairwise comparisons between dose groups were significant ($p < 0.05$) with respect to dose-normalized $C_{max}$, $AUC_{0-72\,h}$, and $AUC_{\infty}$, the magnitude of the difference across the dose range was $<20\%$ for $AUC_{0-72\,h}$ and $AUC_{\infty}$, and was $\leqslant 30\%$ for $C_{max}$. The results indicate a consistent and predictable increase in metformin exposure with an extended-release formulation of metformin over 1000 to 2500 mg. Copyright © 2004 John Wiley & Sons, Ltd.

**Key words:** metformin; extended-release formulation; tolerability; pharmacokinetics; dose proportionality

## Introduction

Metformin has been widely used in the management of type 2, non-insulin-dependent diabetes mellitus (NIDDM). Immediate-release (IR) metformin is administered in divided doses with meals to minimize gastrointestinal side effects [1,2]. A dose of 0.5 g has an oral bioavailability of approximately 50%, with proportionally more drug being absorbed after a 0.5 g dose than after higher doses [2–4].

An extended-release dosage form of metformin (ER-metformin) was developed by Andrx, utilizing the company's patented and proprietary single composition osmotic tablet (SCOT™) technology. The current study was designed to assess the pharmacokinetics and proportionality relationship of 1000, 1500, 2000 and 2500 mg of ER-metformin.

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## Materials and Methods

This was a single-dose, open-label, randomized, four-period crossover study. Twenty-four subjects were enrolled in the study based on inclusion/exclusion criteria for healthy male volunteers. Subjects received the following four metformin doses in random order according to assigned sequences: 1000 mg ($1 \times 1000$ mg tablet), 1500 mg ($1 \times 1000$ mg + $1 \times 500$ mg tablets), 2000 mg ($2 \times 1000$ mg tablets) and 2500 mg ($2 \times 1000$ mg + $1 \times 500$ mg tablets). Each treatment was separated by a 7-day washout period. The treatments were administered

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immediately following a standardized dinner with 240 ml of ambient-temperature water.

Blood samples (10 ml) were collected in heparinized vacutainer tubes at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 38, 48 and 72 h after dosing, for the purpose of quantitating the concentration of metformin in plasma. Plasma samples were assayed using a high-performance liquid chromatographic (HPLC) assay with ultraviolet detection. The standard curves for metformin covered a range of 10–2500 ng/ml; the lower limit of quantitation (LOQ) was 10 ng/ml. Quality control standards (25, 160 and 1600 ng/ml) and the LOQ were used to assess the interday and intraday assay precision and accuracy during validation. The interday assay coefficient of variation (precision) ranged from 4.82% to 8.23% and the percent difference from theoretical (accuracy) ranged from –2.08% to 2.72%, while the intraday precision ranged from 6.16% to 9.56% and accuracy ranged from –17.7% (at the LOQ) to 5.76%.

Pharmacokinetic parameters for metformin included the maximum observed concentration ($C_{max}$), time at which $C_{max}$ occurred ($T_{max}$), lag time ($T_{lag}$) and area under the plasma concentration-time curve (*AUC*). AUC was calculated using the linear trapezoidal rule from time zero to 72 h ($AUC_{0–72h}$). AUC from time zero to infinity ($AUC_{\infty}$) was equal to the sum of $AUC_{0-t}$ and $C(t)/ke$, where $C(t)$ was the plasma concentration at 72 h and *k*e was the terminal elimination rate constant. The terminal elimination half-life ($t_{1/2}$) was calculated as ln(2)/*k*e, and *k*e was determined from linear regression of the terminal portion of the ln-concentration *versus* time curve.

Summary statistics for pharmacokinetic and safety data were generated. Dose proportionality was assessed by comparing dose-normalized pharmacokinetic parameters (*AUC* and $C_{max}$) using a statistical model that included variables for period, dose, and sequence of administration, as well as linear regression analysis of *AUC* or $C_{max}$ and dose.

## Results

Twenty-four healthy males were enrolled and included in the safety assessment. Twenty-three subjects (96%) completed the study and were included in pharmacokinetic and dose proportionality assessment. One subject withdrew consent for personal reasons.

There were no serious adverse experiences during the course of the study. There were nine treatment-emergent signs or symptoms (TESS) that were considered possibly related to treatment.

The plasma metformin concentration time profiles were determined for each subject ($n$=23) at each dose level. Mean ( $\pm$ SD) metformin pharmacokinetic parameters are summarized in Table 1. In the majority of subjects, extrapolation from $AUC_{0–72h}$ to $AUC_{\infty}$ was less than 5%, resulting in reliable estimates of $AUC_{\infty}$. The results of the dose-proportionality assess-

Table 1. Metformin pharmacokinetic parameters (mean $\pm$ SD) and dose-proportionality analysis following a single oral dose

| | Metformin dose | | | | Dose normalized (DN)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| Parameter | 1000 mg | 1500 mg | 2000 mg | 2500 mg | 1000 mg | 1500 mg | 2000 mg | 2500 mg |
| $C_{max}$ (μg/ml) | 1.42 $\pm$ 0.32 | 1.78 $\pm$ 0.37 | 2.11 $\pm$ 0.52 | 2.48 $\pm$ 0.53 | 1.42[c] | 1.19[c] | 1.05[d] | 0.99[e] |
| $AUC_{0-72h}$ (μg h/ml) | 11.90 $\pm$ 2.76 | 16.68 $\pm$ 4.14 | 20.65 $\pm$ 3.82 | 24.18 $\pm$ 3.97 | 11.87[c] | 11.10[c] | 10.30[d] | 9.65[e] |
| $AUC_{\infty}$ (μg h/ml) | 11.94 $\pm$ 2.71 | 16.70 $\pm$ 4.15 | 20.81 $\pm$ 3.87 | 24.26 $\pm$ 4.10 | 11.91[c] | 11.11[c] | 10.38[d] | 9.71[e] |
| $T_{max}$ (h) | 6.3 $\pm$ 1.4 | 6.7 $\pm$ 1.6 | 7.8 $\pm$ 2.0 | 7.2 $\pm$ 2.1 | – | – | – | – |
| $T_{lag}$ (h) | 0.4 $\pm$ 0.5 | 0.3 $\pm$ 0.6 | 0.2 $\pm$ 0.4 | 0.0 $\pm$ 0.0 | – | – | – | – |
| $t_{1/2}$ (h)[a] | 5.0 | 5.6 | 7.4 | 7.5 | – | – | – | – |

[a] Harmonic mean.
[b] Least-squared mean (LSM) estimates of pharmacokinetic parameters were dose normalized to 1000 mg.
[c] There is a statistical difference ($p<0.05$) in DN LSM between dose group and other three dose groups.
[d] There is a statistical difference ($p<0.05$) in DN LSM between dose group and two dose groups (1000 mg and 1500 mg), however, there is no difference ($p>0.05$) from 2500 mg dose group.
[e] There is a statistical difference ($p<0.05$) in DN LSM between dose group and two dose groups (1000 mg and 1500 mg), however there is no difference ($p>0.05$) from 2000 mg dose group.

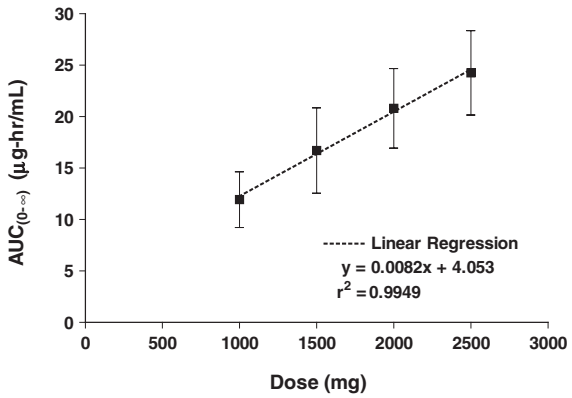


Figure 1. Relationship between mean (SD) ER-metformin $AUC_{(0-\infty)}$ and dose

ment are also shown in Table 1. All pairwise comparisons between doses were significant ($p < 0.05$) with respect to dose-normalized $C_{max}$, $AUC_{0-72h}$ and $AUC_{\infty}$ except for the comparisons between the two highest doses. The magnitude of the differences across the dose range was on average $\leqslant 30\%$ for $C_{max}$ and $<20\%$ for both $AUC_{0-72h}$ and $AUC_{\infty}$. There was no detectable difference in model-independent pharmacokinetic parameters including $T_{max}$ and half-life ($t_{1/2}$) among the doses. The linear regression of the mean values of the four treatments resulted in a coefficient-of-determination ($r^2$) that was >0.99 for $C_{max}$, $AUC_{0-72h}$ and $AUC_{\infty}$, and deviation from zero was significant ($p < 0.05$) for all three parameters. The linear regression for $AUC_{\infty}$ is shown in Figure 1.

Although considerable overlap in exposure was observed, there was a predictable and consistent dose-associated increase in metformin exposure as represented by $C_{max}$, $AUC_{0-72h}$, and $AUC_{\infty}$. The dose-exposure relationship is particularly noteworthy for $AUC_{\infty}$ (Figure 1) whereby the least-squares means for the 1500, 2000 and 2500 mg doses were all within 20% of the values dose-normalized to 1000 mg (Table 1).

## Discussion/Conclusion

The pharmacokinetic properties of metformin have been investigated using a variety of formulations including intravenous and oral aqueous solution, rapidly dissolving tablets, and modified-release formulations [1,2,5,6]. Generally, the pharmacokinetics of metformin are characterized by slow and incomplete (40%–60%) absorption in combination with rapid elimination [1,2]. Although oral absorption has been estimated to be complete within 6 h of administering IR-metformin, the lack of dose-proportionality at doses higher than 500 mg suggests the possible involvement of a saturable absorption process, which might significantly limit oral absorption at higher doses [1,2,7].

In the current study the extended-release tablets developed by Andrx showed no evidence that metformin bioavailability was impaired at such high doses. On the contrary, there was a consistent and predictable dose-associated increase in metformin exposure with increasing dose. The results of this study therefore would support the assertion from an earlier trial that a large segment of the intestine can be involved in the absorption of metformin [2,8]. In conclusion, this study demonstrated that there was a predictable and consistent dose-associated increase in metformin exposure within the dose range 1000–2500 mg with an extended-release formulation of metformin.

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