Delayed-Release Metformin May be Suitable for Use in Diabetes Patients with Renal Impairment Who are Contraindicated for Currently Available Metformin Formulations

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Summary and Conclusions

- **Delivery of 1000 mg and 2000 mg/day metformin to the lower bowel using a delayed-release formulation resulted in substantial reductions in plasma metformin exposure (45% - 68%) compared to 2000 mg/day Met IR and Met XR without negatively affecting its glucose-lowering capacity (See ADA Poster 1087-P for complete summary).**
- **A population PK model was used to determine if the reductions in metformin exposure observed with Met DR were sufficient to justify its use in patients with renal impairment, a population at risk for lactic acidosis due to plasma metformin accumulation.**
  - **Results of the model predict that 2000 mg/day and 1000 mg/day Met DR in patients with severe renal impairment would result in lower peak and total plasma metformin exposure than maximally effective doses of Met XR or Met IR in patients with normal renal function.**
- **Met DR may therefore be an effective way of providing metformin to patients with type 2 diabetes and renal impairment without increasing the risk of lactic acidosis.**
- **Since 1000 mg/day Met DR had lower exposure but equal glucose-lowering effects as 2000 mg/day Met DR, the 1000 mg/day Met DR dose provided the most favorable benefit-risk profile of the doses studied.**
- **Additional studies are underway to determine the effects of lower doses of Met DR (<1000 mg/day) over 12 weeks and to validate exposure predictions in patients with renal impairment.**

Abstract

We recently uncovered that metformin's (Met) glucose-lowering effects are predominantly due to actions on enteroendocrine L-cells which are more densely populated in the lower bowel and that plasma Met exposure is not required for efficacy. Met is contraindicated in patients with renal impairment due to Met accumulation and associated risk of lactic acidosis. By targeting a daily dose of 1000 mg delayed-release metformin (Met DR) directly to the lower bowel of patients with type 2 diabetes, Met exposure was reduced by 68% relative to a daily dose of 2000 mg immediate release Met (Met IR). Despite lower Met exposure, Met DR produced a similar glucose lowering effect as Met IR and increased fasting and postprandial plasma GLP-1 and PYY concentrations. We hypothesized that Met DR may be a viable treatment for diabetic patients with renal impairment. We used a population PK model based on data from 2 clinical studies (N=44) of Met DR, Met IR, and Met extended-release (Met XR) to predict Met exposure (AUC 0-48 h) following administration of each formulation in normal patients and those with varying degrees of renal impairment (mild to severe). The median predicted AUCs (ng*h/ml) for 1000 mg daily Met DR in patients with normal, mild, moderate and severe renal impairment were 4669, 4984, 5524, and 6527. Predicted AUCs (ng*h/ml) were significantly higher for 2000 mg daily Met IR and Met XR (22659 and 20607 with normal renal function and 31606 and 29074 with severe renal impairment). Thus, in patients with severe renal impairment, 1000 mg daily Met DR is predicted to result in lower plasma Met exposure than 2000 mg daily Met IR or Met XR in patients with normal renal function, while maintaining comparable glucose-lowering efficacy. Met DR may provide a method to treat renally impaired type 2 diabetic patients with metformin without increasing the risk of Met associated lactic acidosis.

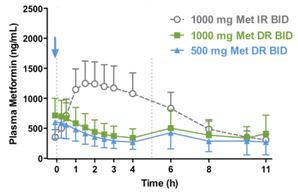
Presented at the 73rd Annual Scientific Meeting of The American Diabetes Association, June 21-25th, 2013, in Chicago, IL.

Introduction

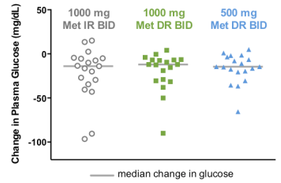
- Metformin is the most commonly prescribed treatment for type 2 diabetes in the world, however the mechanism for its glucose-lowering action remains poorly understood.
- Metformin is cleared by the kidneys and the half-life of metformin is prolonged in patients with renal impairment[1].
- Metformin is contraindicated in individuals with moderate to severe renal impairment because of increased risk of lactic acidosis caused by increased plasma metformin concentrations[1].
- We recently uncovered that metformin's glucose-lowering effects do not require plasma metformin exposure and may result from a pre-systemic effect on enteroendocrine L-cells in the distal small and large intestine to stimulate release of gut hormones[2,3].
- A novel, delayed-release metformin formulation, Met DR, was designed to minimize metformin exposure by bypassing the highly absorptive upper bowel and delivering metformin to the distal small intestine where metformin is poorly absorbed and L-cells are more densely located.

- **Since the entire dose of Met DR is delivered to the site of action (lower bowel), smaller metformin doses maintained the glycemic effect of a maximum dose of commercially available metformin formulations: immediate-release (Met IR) and extended-release metformin (Met DR) (See ADA Poster 1087-P for complete summary).**

Lower Metformin Exposure with Met DR Relative to Met IR After 5 Days of Treatment



Similar Reduction in Plasma Glucose After 5 days of Met IR or Met DR



Evaluable population. Data are mean and SD (left) and individual and median change in fasting plasma glucose from baseline to Day 5 (right). All treatments (blue arrow) were administered at t = -1 min. Vertical grey dotted lines indicate ~500 kcal breakfast (t=0 h) and ~1000 kcal lunch (t=5h).

- 1000 or 2000 mg/day Met DR resulted in a 45% to 68% reduction in plasma metformin exposure relative to 2000 mg/day Met IR and Met XR.
  - 1000 mg/day of Met DR was maximally effective:
    - 1000 and 2000 mg/day Met DR produced similar reductions in fasting and postprandial glucose as 2000 mg/day Met IR.
    - 1000 and 2000 mg/day Met DR produced similar increases in fasting and postprandial glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) as 2000 mg/day of Met IR.

References

1. Glucophage (metformin hydrochloride) and Glucophage XR (extended-release) Prescribing Information. In. Bristol, NJ: Bristol-Myers Squibb; 2009.
2. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574-9.
3. Neary MT, Batterham RL. Gut hormones: implications for the treatment of obesity. Pharmacol Ther 2009;124:44-56.
4. Taylor A, Chigusta E, Monteleone J, Fineman MS. Population Pharmacokinetic Modeling of a Novel Delayed-Release Formulation of Metformin (MetDR), W-002. In: American Conference on Pharmacometrics. Fort Lauderdale, FL; May 12-15, 2013.

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Hypothesis

Due to lower plasma metformin exposure relative to currently available metformin formulations (Met IR and Met XR), Met DR may be a viable treatment for type 2 diabetes patients with renal impairment without increasing the risk of metformin-associated lactic acidosis.

Objective

To predict whether the maximally effective dose of Met DR (1000 mg/day) may be safe to use in patients with renal impairment based on predicted plasma metformin concentrations in patients with mild, moderate, and severe renal impairment.

Methods: Plan to Simulate Metformin Exposure

1 Develop Population PK (PPK) Model

Develop a PPK model (using PK data from patients with normal renal function and mild renal impairment) to simulate plasma metformin exposure across a range of doses, formulations (Met DR, Met IR, and Met XR) and degrees of renal impairment.

2 Predict Safe Metformin Exposure Threshold

Determine a safe threshold for plasma metformin concentrations (AUC and C_{max}) based on simulated exposures with Met IR and XR when used according to the label (approved doses in patients with normal renal function), ie, exposures in clinical practice.

3 Predict Metformin Exposure with Met DR in Patients with Renal Impairment

Use PPK model to predict plasma metformin exposure (AUC and C_{max}) in patients with mild, moderate, and severe renal impairment following administration of Met DR doses of 1000 and 2000 mg/day.

4 Compare Predicted Metformin Exposures

Compare predicted plasma metformin exposure for Met DR among patients with normal renal function and mild, moderate, and severe renal impairment to the established safe threshold of plasma metformin that occurs in clinical practice.

PPK Model Development

- The PPK model was developed based on data from the following 2 crossover studies of Met DR, Met IR, and Met XR (N=44):

	Single Daily Dose Study	Steady State (5 day) Study
Study Design	Randomized, crossover study in healthy volunteers	Randomized, crossover study in patients with type 2 diabetes*
Treatments	1000 mg Met IR BID	1000 mg Met IR BID
	1000 mg Met DR BID	1000 mg Met DR BID
	500 mg Met DR BID	500 mg Met DR BID
	2000 mg Met XR QD	

*Patients were taken off any diabetes medications 2 weeks before study.

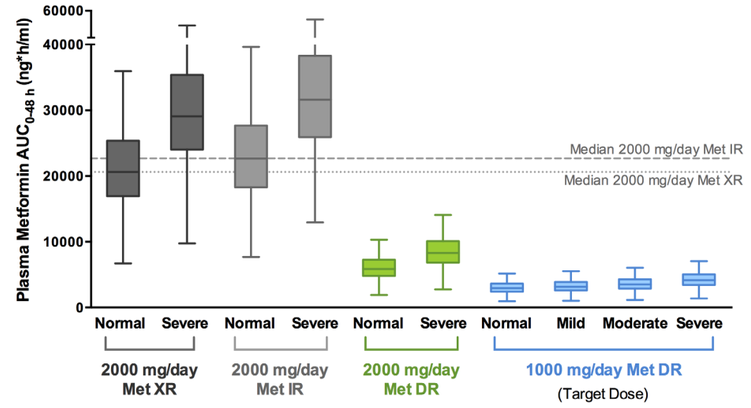
- Nonlinear regression analysis with NONMEM (v7.2) was used to fit the model and the final model was selected based on standard diagnostics including goodness of fit plots and the minimum value of the objective function.
- The developed PPK model was used to link dose to blood levels of metformin, which could then be used to calculate $AUC_{0\text{-}48\ h}$ and C_{max} to determine the impact of formulation on metformin exposure.
- Details of model development have been described previously[4].

Dosing Simulations

- To determine a threshold plasma exposure of metformin that is considered to be safe as defined in the label (approved doses in patients with normal renal function), plasma metformin exposures were simulated for typical doses of Met IR and Met XR (2000 mg/day) in patients with normal renal function. These values represent typical metformin exposures observed in clinical practice when administered according to the current metformin label.
- For the basis of comparison, plasma exposures for 2000 mg/day Met IR and Met XR were also simulated in patients with severe renal impairment. These values represent metformin exposures that should not occur in clinical practice due to metformin contraindication in renal impairment.
- Met DR doses of 1000 and 2000 mg/day were simulated in patients with normal renal function and patients with mild, moderate, and severe renal impairment.
- Monte Carlo simulations were performed using NONMEM by randomly sampling the PPK model parameters to predict concentration-time profiles for 1,000 virtual patients.
- The recommended dosing regimens from the Met IR and Met XR labels were used for all simulations: Met IR = BID with morning and evening meals; Met XR = QD with the evening meal. Simulations with Met DR used QD administration with the morning meal.
- The concentration-time profiles were then used to calculate $AUC_{0\text{-}48\ h}$ and C_{max} for each patient under different dose, formulation, and renal impairment conditions (defined as creatinine clearance rate of 25, 50, 75, or 100 ml/min).

Results: Predicted Total and Peak Metformin Exposure: Normal vs. Impaired Renal Function

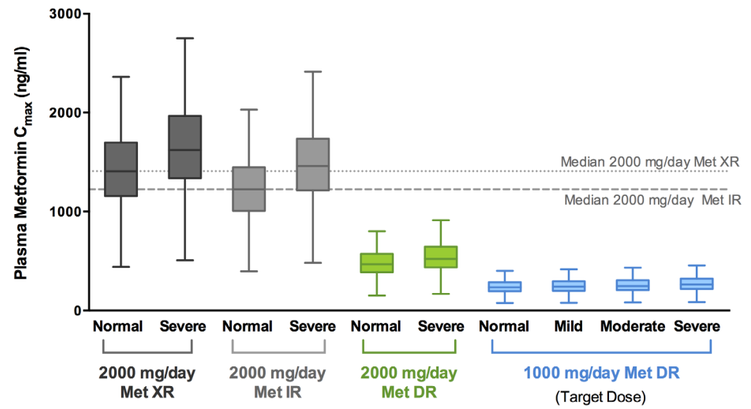
Lower Metformin AUC with Met DR Relative to Met XR and Met IR



Data are median, 25th and 75th percentiles, and 5th and 95th percentiles for simulated median metformin exposures in patients with normal renal function or mild, moderate, or severe renal impairment. Dotted line represents the median predicted exposures with 2000 mg/day Met XR in patients with normal renal function. Dashed line represents the median predicted exposures with 2000 mg/day Met IR in patients with normal renal function. All doses are in mg/day.

Treatment (mg/day)	2000 mg Met XR		2000 mg Met IR		2000 mg Met DR		1000 mg Met DR			
Renal Function/Impairment	Normal	Severe	Normal	Severe	Normal	Severe	Normal	Mild	Moderate	Severe
Predicted AUC (ng*h/ml)										
Median	20607	29074	22659	31606	5872	8287	2936	3152	3497	4144
25th, 75th Percentile	16915, 25361	24032, 35368	18292, 27668	25922, 38278	4813, 7235	6846, 10077	2407, 3618	2595, 3882	2880, 4267	3423, 5039
5th, 95th Percentile	6719, 35946	9742, 49098	7687, 39643	12931, 53492	1904, 10298	2760, 14062	952, 5149	1028, 5501	1146, 6032	1380, 7031

Lower Metformin C_{max} with Met DR relative to Met XR and Met IR



Data are median, 25th and 75th percentiles, and 5th and 95th percentiles for simulated median metformin exposures in patients with normal renal function or mild, moderate, or severe renal impairment. Dotted line represents the median predicted exposures with 2000 mg/day Met XR in patients with normal renal function. Dashed line represents the median predicted exposures with 2000 mg/day Met IR in patients with normal renal function. All doses are in mg/day.

Treatment (mg/day)	2000 mg Met XR		2000 mg Met IR		2000 mg Met DR		1000 mg Met DR			
Renal Function/Impairment	Normal	Severe	Normal	Severe	Normal	Severe	Normal	Mild	Moderate	Severe
Predicted C_{max} (ng/ml)										
Median	1408	1620	1224	1459	467	523	234	240	248	262
25th, 75th Percentile	1156, 1697	1337, 1966	1008, 1447	1212, 1734	387,573	435, 646	194, 286	199, 295	206, 306	218, 323
5th, 95th Percentile	441, 2360	507, 2751	396, 2029	479, 2412	150, 801	168, 912	75, 401	77, 415	80, 432	84, 456

- The median predicted exposures with Met XR and Met IR in patients with normal renal function represent safe levels of metformin in clinical practice where the reported incidence of lactic acidosis is very low.
- In patients with any degree of renal impairment, predicted total and peak metformin exposures ($AUC_{0\text{-}48\ h}$ and C_{max}) with 1000 and 2000 mg/day Met DR were significantly lower than with 2000 mg/day Met XR or IR in patients with normal renal function.