PERSPECTIVE

Oral Glucose Tolerance Test: An Informative Endpoint or an Added Burden in Metformin Drug–Drug Interaction Studies?

Anees M. Dauki[1], Chia-Hsiang Hsueh[1,†], Ganesh Cherala[1,†] and Ahmed A. Othman[1,*]

For drugs that inhibit organic cation transporters and/or multidrug and toxin extrusion proteins, a metformin clinical drug–drug interaction (DDI) study is recommended to assess the impact on metformin's systemic exposure. An oral glucose tolerance test (OGTT) has been proposed as an additional end point to evaluate potential changes in metformin's efficacy when OCT1 inhibition is suspected. Here, we discuss the limitations of the OGTT in healthy volunteers DDI studies.

Metformin is a metabolically stable drug that is primarily cleared by glomerular filtration and tubular secretion and is a substrate for the organic cation transporter (OCT)-2 and multidrug and toxin extrusion (MATE)-1 and 2K transporters. A metformin clinical pharmacokinetic drug–drug interaction (DDI) study is typically recommended for drugs that inhibit OCT2/MATE1/2-K. Systemic exposure of metformin, in conjunction with its renal clearance, are often used as end points in such clinical DDI studies.

Metformin is also a substrate for OCT1 and its pharmacodynamic effect is mediated by hepatic uptake via OCT1. Inhibition of OCT1 may alter metformin's efficacy without impacting its systemic exposure.[1] Therefore, metformin's systemic exposure may not fully inform the need for dose adjustments when OCT1 inhibition is suspected. To overcome this limitation, several metformin clinical DDI studies have incorporated an oral glucose tolerance test (OGTT) as an additional end point. Furthermore, a recent commentary from the International Transporter Consortium proposed detailed metformin DDI study design incorporating this additional end point.[2] The sound scientific rationale coupled with the opportunistic nature of the additional end point is compelling, however, the limitations of conclusions from the OGTT assessment in healthy volunteers might limit its utility. Here, we summarize the limitations of OGTT in healthy volunteers clinical DDI study setting.

OGTT IS VARIABLE WITH POOR REPRODUCIBILITY

The OGTT has been in use for more than 100 years and has evolved considerably over the course of time. Considerable efforts were made to simplify OGTT and decrease its variability. Among elderly White subjects, intra-individual variability in OGTT was reported to be ~17% due to biological variability.[3] A systematic decrease of the plasma glucose values upon retests was observed and the magnitude of this decrease varied across studies.[3] In an epidemiological study conducted in Tanzania, the variability in OGTT was larger with an age effect where younger subjects experienced greater difference between test and retest.[4] The age effect on OGTT variability is worth noting given that it may confound extrapolation of DDI results from young adults often recruited in healthy volunteer DDI studies to older patients with diabetes mellitus (DM).

HEALTHY VOLUNTEERS ARE NOT REPRESENTATIVE OF PATIENTS WITH DM

The OGTT was initially developed as a diagnostic test for DM.[5] Recently OGTT has been utilized in a few healthy volunteer DDI studies assessing the effect of perpetrator drugs on renal transporters to inform metformin dose adjustment. However, assessment of metformin's pharmacodynamic effect in healthy volunteers may not be informative for such effect in patients with DM. Specifically, healthy volunteers and patients with DM exhibit different baseline blood glucose levels and different magnitudes of blood glucose fluctuations.

[1]Gilead Sciences, Inc., Foster City, California, USA. *Correspondence: Ahmed A. Othman (ahmed.othman@gilead.com)
[†]Affiliation at the time this research was conducted.

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As OGTT evaluates the effect of carbohydrate ingestion on blood glucose fluctuations, differences in the baseline level and response hinder the extrapolation of data collected in healthy volunteers to patients with DM. Sambol *et al*.[6] reported differential metformin effects on glucose/insulin response by meal between age-matched healthy volunteers and patients with non-insulin dependent DM despite similar metformin exposure. Additionally, the dose-dependent effect of metformin on post-prandial glucose fluctuations was observed in patients with non-insulin dependent DM but not in healthy volunteers after administration of 850–2,550 mg metformin single doses.[6] This may be due to the variability and the narrower dynamic range of the OGTT in healthy volunteers; limiting the utility of the OGTT in healthy volunteer DDI studies.

Inconsistent OGTT responses were observed in DDI studies evaluating the interaction between metformin and rifampin in healthy volunteers[7] versus in patients with DM[8]; rifampin increased metformin exposure in both healthy volunteers and in patients with DM but only altered (increased) the glucose lowering effect of metformin in healthy volunteers. Overall, despite the limited data informing the extrapolation of OGTT data from healthy volunteers to patients with DM, current evidence suggests limited predictive value of such extrapolation.

OCT1 IS HIGHLY POLYMORPHIC

OCT1 is encoded by solute carrier family 22 member 1 (SLC22A1) which is in chromosome 6 and encodes OCT1 11 exons. Several alternatively spliced mRNA isoforms can be produced from SLC22A1 pre-mRNA. Multiple studies showed associations between genetic polymorphisms of SLC22A1 and metformin disposition, efficacy, and safety profiles.[9] Notably, five variants (rs34130495, rs12208357, rs72552763, rs34059508, and rs622342) are associated with reduced transporter uptake activity.[9] Therefore, if OGTT is to be implemented as an end point in clinical DDI studies, the polymorphic nature of OCT1 and the potential impact on OGTT variability and response need to be accounted for in the study design, including considerations for the sample size and pharmacogenetic testing for OCT1 polymorphism in evaluated subjects to aid in interpretation of the data.

UTILITY OF OGTT IN HEALTHY VOLUNTEERS TO ULTIMATELY INFORM METFORMIN DOSE ADJUSTMENTS IN PRESCRIBING INFORMATION IS UNCLEAR

The addition of OGTT in the metformin DDI study aims to explore the potential of reduced metformin efficacy as a result of reduced hepatic exposure in the presence of a perpetrator. Given the limitations noted above, it is unclear if a change in OGTT response in healthy volunteer DDI studies can be extrapolated to the patient population or can inform the need for dose adjustment in clinical practice.

Review of DDI studies reported in the University of Washington Drug Interaction Database (DIDB) and the corresponding product labels suggested limited benefit of the OGTT as an end point in healthy volunteers' metformin clinical DDI studies. In the cases where OGTT was included as an end point in metformin DDI studies, its relevance in informing the need, or lack thereof, for dose adjustments in the labels for evaluated drugs was not apparent.

As of February 2, 2022, there were a total of 17 metformin DDI studies that included OGTT assessments reported in the University of Washington DIDB (**Table S1**). Five of these 17 studies reported somewhat altered metformin pharmacokinetics as a result of interactions with the evaluated drugs, but no effect on metformin's OGTT response. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) increased metformin exposure by ~40% but had no effect on the OGTT response in healthy volunteers. Despite the lack of OGTT effect in healthy volunteers, bictegravir/emtricitabine/tenofovir alafenamide's United States prescribing information (USPI) refers to metformin's prescribing information for assessing the benefit and risk of concomitant use of bictegravir/emtricitabine/tenofovir alafenamide with metformin. Rifampin increased metformin exposure by 13% with no impact on metformin's OGTT response in healthy volunteers. The USPI of rifampin recommends using rifampin with caution in patients with DM, as diabetes management may be more difficult with rifampin concomitant use because rifampin is known to alter blood glucose concentrations. Whether an OGTT is performed or not in healthy volunteers, it seems that the pharmacokinetic DDI or other known relevant pharmacodynamic impact ends up being the driver of the label language, and lack of an effect on OGTT in healthy volunteers does not seem to contribute to informing the label. The other three studies showed small changes in exposure of metformin by the perpetrator drugs, and no effect on the OGTT response was observed. As expected, neither the pharmacokinetic nor the OGTT results are described in the respective drug labels.

The study that suggested altered metformin OGTT response without a change in metformin systemic exposure was with verapamil as a perpetrator.[10] Verapamil was reported to inhibit the ability of metformin to reduce maximum blood glucose concentrations (ΔG_{max}) by 62.5% and decreased the area under the glucose concentration–time curve (ΔAUC_{gluc}) by 238%. Verapamil-metformin pharmacodynamic interaction (OGTT) is not currently described in verapamil's USPI.

Overall, caution needs to be taken whenever a perpetrator increases metformin systematic exposure and conclusions based on metformin's OGTT response in healthy volunteers that do not seem to have an impact in informing the drug labels.

CONCLUDING REMARKS

In our view, OGTT as an additional end point in metformin clinical DDI studies in healthy volunteers is of limited value. The small dynamic range of OGTT coupled with variability in response in healthy volunteers, and the lack of quantitative correlation to potential effect in patients reduce the ability to extrapolate the results of OGTT effect from healthy volunteers to inform dosing recommendations or need for metformin dose adjustments in patients with DM. As such, metformin healthy volunteer DDI studies shall be focused on assessing the pharmacokinetic interaction. If a pharmacodynamic interaction that is not driven by alterations in plasma metformin exposure is suspected, drug interaction studies with the proper design in patients with DM may be

warranted and the OGTT can be considered as an end point in these studies.

SUPPORTING INFORMATION

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CONFLICT OF INTEREST

A.D. and A.O. are employees of, and may own stocks in, Gilead Sciences, Inc. C.-H.H. and G.C. are previous employees of Gilead Sciences and may own stocks in Gilead Sciences, Inc.

1. Shu, Y. *et al*. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J. Clin. Invest.* **117**, 1422–1431 (2007).
2. Zamek-Gliszczynski, M.J. *et al*. ITC commentary on metformin clinical drug-drug interaction study design that enables an efficacy- and safety-based dose adjustment decision. *Clin. Pharmacol. Ther.* **104**, 781–784 (2018).
3. Mooy, J.M. *et al*. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn study. *Diabetologia* **39**, 298–305 (1996).
4. Swai, A.B. *et al*. Study in Tanzania of impaired glucose tolerance. Methodological myth? *Diabetes* **40**, 516–520 (1991).
5. Harlass, F.E. *et al*. Use of a standard preparatory diet for the oral glucose tolerance test. Is it necessary? *J. Reprod. Med.* **36**, 147–150 (1991).
6. Sambol, N.C. *et al*. Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *J. Clin. Pharmacol.* **36**, 1012–1021 (1996).
7. Cho, S.K. *et al*. Rifampin enhances the glucose-lowering effect of metformin and increases OCT1 mRNA levels in healthy participants. *Clin. Pharmacol. Ther.* **89**, 416–421 (2011).
8. Te Brake, L.H.M. *et al*. Rifampicin alters metformin plasma exposure but not blood glucose levels in diabetic tuberculosis patients. *Clin. Pharmacol. Ther.* **105**, 730–737 (2019).
9. Ahlin, G. *et al*. Genotype-dependent effects of inhibitors of the organic cation transporter, OCT1: predictions of metformin interactions. *Pharmacogenomics. J.* **11**, 400–411 (2011).
10. Cho, S.K. *et al*. Verapamil decreases the glucose-lowering effect of metformin in healthy volunteers. *Br. J. Clin. Pharmacol.* **78**, 1426–1432 (2014).