Effects of dextromethorphan as add-on to sitagliptin on blood glucose and serum insulin concentrations in individuals with type 2 diabetes mellitus: A randomized, placebo-controlled, double-blinded, multiple cross-over, single-dose clinical trial

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ABSTRACT

In a recent clinical trial we showed that the NNDA receptor antagonist dextromethorphan (DXM) enhanced postprandial serum insulin concentrations and lowered blood glucose (BG) concentrations in individuals with type 2 diabetes mellitus (T2DM). In this clinical trial, we investigated the BG-lowering effects of 30-90 mg DXM and 100 mg sitagliptin (Sita), a dipeptidylpeptidase-4 (DPP-4) inhibitor, alone versus combinations of DXM and Sita during an oral glucose tolerance test in 20 male individuals with T2DM. The combination of 60 mg DXM and 100 mg Sita improved maximum BG and postprandial serum insulin concentrations to a significantly larger extent compared to 100 mg Sita and 60 mg DXM alone. All study drugs were well tolerated, alone and in combination, without serious adverse events or hypoglycemia. The findings suggest that addition of DXM to a therapy with DPP-4 inhibitors or incretins could be beneficial for individuals with T2DM and warrant long-term clinical trials.

INTRODUCTION

Recently we observed that the over-the-counter medication DXM increased postprandial serum insulin concentrations and lowered BG excursions (Marquard et al., NMED 2015; Maechler & Wollheim, NMED 2015). Similarly, DPP-4 inhibitors, such as Sita, enhance postprandial serum insulin concentrations and blood glucose control, but in contrast to DXM, are established anti-diabetic drugs (Bo Ahren, Diabetes Metab Syndr Obes 2010; Rosenstock & Zinman, Curr Opin Endocrinol Diabetes Obes 2007; Cefalu...Riddle, Diabetes Care 2014). Since both DPP-4 inhibitors and DXM do not introduce severe hypoglycemic events, have few adverse effects in general and are orally applied, we now investigated in a phase-2a clinical trial the effects of DXM and Sita alone, and in combination, on BG and serum insulin concentrations in individuals with T2DM.

RESEARCH DESIGN AND METHODS

Trial design

Male individuals with T2DM on a stable metformin monotherapy were screened for participation and randomized to receive 30, 60 or 90 mg DXM alone or in combination with 100 mg Sita each, 100 mg Sita alone, or placebo (for DXM and Sita) on a total of eight treatment days according a randomization scheme (Suppl. Fig. 1). The OGTT was started after fasting overnight and one hour after study drug administration (time point: 1 h). Blood was taken from before to six hours after administration of the study drugs. The OGTT was performed with 75 g glucose (Accu-Chek Dextro O.G.-T., Roche Diagnostics, Germany), and BG samples were analyzed using the glucose analyzer Super GL (Dr. Müller Gerätebau GmbH).

Participants

Eligible subjects were male individuals with a diagnosis of T2DM according to ADA criteria at least 4 months prior to screening and on a stable regimen of metformin monotherapy, for at

least 3 months, medical history without major pathology (with the exception of T2DM), age between 45 and 70 years, body mass index (BMI) between 25 and 35 kg/m^2 and $HbA_{1c} \geq 6.5$ and $\leq 8.0\%$ (Suppl. Table 1). The study was conducted at the Profil Institute for Metabolic Research, Neuss, Germany.

Interventions

Individuals received study medication on eight treatment days with a 7 to 14-day washout period between. One hour after study drug administration,,an OGTT was started and blood was drawn every 15 to 90 minutes over the following 5 h Sitagliptin phosphate monohydrate (100 mg tablets; MSD Sharp & Dohme GmbH; Januvia®), Sita placebo tablets (P-tablets white 10 mm Lichtenstein, Winthrop Arzneimittel GmbH), dextromethorphan hydrobromide monohydrate (30 mg hard capsules; Ratiopharm GmbH; Hustenstiller-ratiopharm®), and DXM placebo hard capsules (empty capsules, Capsugel Bornem, Belgium) were provided in HDPE containers and taken with a glass of tap water (approximately 240 ml).

Outcomes

The first primary objective of this clinical trial was to find the lowest dose of DXM that, compared to placebo, exerts BG lowering effects related to the OGTT. The second primary objective was to investigate whether a low dose of DXM on top of Sita exerts additive BG lowering effects related to an OGTT compared to Sita alone and DXM alone. The primary pharmacodynamic (PD) parameter was the area under the curve (AUC) of BG concentrations from 0-2 hours after starting the OGTT, AUC Glucose 1-3 h..Secondary PD parameters were among others: AUC Glucose 0-1 h , AUC Glucose 1-5 h, Max. Glucose (i.e. the maximum BG concentration after starting the OGTT), AUC Insulin 0-1 h, AUC Insulin 1-1.5 h, AUC Insulin 1-3 h, AUC Insulin 1-5 h, and Max. Insulin. The insulin parameters were adjusted to baseline insulin levels. AUC Glucagon 0-1 h, AUC Glucagon 1-3 h, AUC Gucagon 1-5 h, and Max. Glucagon were determined for placebo, Sita, 60 mg DXM (DXM 60), and 60 mg DXM

plus Sita (DXM 60 + Sita). PD parameters were determined as previously described (cite Marquard et al., NMED)

Sample size

For the primary PD endpoint, a mean difference of at least 10% in AUC Glucose 1-3 h was considered to be clinically relevant. For a significance level alpha of 5%, a sample size of 20 subjects completing the study was calculated to provide a power of approximately 80% to detect such difference.

Randomization

Each subject received each of the 8 possible treatments according to a randomization scheme. The randomization list was computer generated by the Profil Institute for Metabolic Research using the randomization system RANCODE Professional 3.6. The unblinded person was informed of that randomization number in order to prepare and dispense the appropriate treatment.

Statistical analyses

Sequence generation , Allocation concealment mechanism, Implementation

Blinding

Study medication was administered in a double-blind manner

RESULTS

20 male individuals with T2DM on metformin monotherapy,(mean HbA_{1c} of 7.2 ± 0.4%; mean BMI of 30.2 ± 2.6; and mean age of 63.1 ± 7.1 years) completed the clinical trial (Suppl. Tab. 1). After fasting overnight, the individuals received in the morning of each treatment day either 30 mg DXM, 60 mg DXM , 90 mg DXM, 100 mg Sita, 30 mg DXM plus 100 mg Sita, 60 mg DXM plus 100 mg Sita, 90 mg DXM plus 100 mg Sita, or placebo (Suppl. Fig. 1). One hour after study drug administration, an OGTT was performed, and blood

was taken to determine BG, serum insulin, and plasma glucagon concentrations in each individual (Fig. 1a). The 8 treatment days were separated by washout periods of 3-14 days. All doses of DXM alone were found to reduce maximal BG concentrations, AUC Glucose 1-3 h and AUC Glucose 1-5 h compared to placebo (Suppl. Table 2a). Notably, 60 mg DXM alone reduced BG concentrations by around 4% in the first 2 and 4 h after starting the OGTT (Suppl. Table 2a), but the effects did not reach statistical significance (P = 0.09 and 0.06, respectively). At this dose, the number of adverse events was not different from that of placebo (Suppl. Table 3). For comparison, Sita significantly reduced AUC Glucose 1-3 h and AUC Glucose 1-5 h by around 7.2% (P = 0.006) and 6.5% (P = 0.005), respectively. Thus 100 mg Sita was better than 60 mg DXM at reducing BG excursions in individuals with T2DM, but the difference between Sita and DXM was not statistically significant for neither maximal BG concentrations (P = 0.26) nor AUC Glucose 1-3 (P = 0.27) and AUC Glucose 1-5 h (P = 0.27; Fig. 1b; Suppl. Table 2a).

When DXM was used as add-on to Sita, all doses of DXM plus Sita numerically showed lower maximum BG concentrations, AUC Glucose 1-3 h and 1-5 h compared to Sita alone (Suppl. Table 2a). In contrast, virtually no reduction in fasting BG concentrations (Suppl. Table 2b). 60 mg DXM plus Sita was noted to significantly lower maximal BG concentrations compared to Sita alone (P = 0.046; Fig. 1a-c).

Consistent with the observation that DXM enhances glucose-stimulated insulin secretion from human pancreatic islets (Marquard et al., 2015), all doses of DXM plus Sita numerically increased serum insulin concentrations during the first 30 minutes of the OGTT compared to Sita alone (Suppl. Table 2a). This increase was significant for the combination of 30 mg DXM plus Sita and 60 mg DXM plus Sita (P = 0.017 and 0.039, respectively) when compared to Sita alone (Fig. 1d, Suppl. Table 2a). The combination of 30 mg DXM plus Sita and 60 mg DXM plus Sita increased the baseline adjusted AUC Insulin 1-1.5 h by around 115.4% or 107.7%, respectively, versus 48.7% under Sita alone compared to placebo (Fig. 1d,

Suppl. Table. 2a). In contrast, the study medication did not change plasma glucagon concentrations compared to placebo (Suppl. Table 2a).

All doses of study medication were well tolerated (Suppl. Table 3). For example, no adverse events (AEs) were observed under 30 mg DXM plus Sita, and only a mild AE was noted under 60 mg DXM plus Sita.

Finally, whereas each study medication alone, including Sita, failed to reach the primary PD endpoint of this study, that is, a reduction of AUC Glucose 1-3 h by at least 10%, all three combinations of DXM (30, 60 and 90 mg) plus Sita did reached this endpoint. Compared to placebo, these combinations reduced the AUC Glucose 1-3 h by 11.6% - 12.1% (Fig. 1c; Suppl. Table 2a), whereas Sita alone only reduced it by 7.3% (Suppl. Table 2a). A dose dependency was not detected for the primary endpoint, but for AUC Glucose 1-5 h (the blood glucose concentration of the first 4 h after starting the OGTT), the reduction correlates with the dose of DXM to some extent. For 30, 60 and 90 mg DXM added to Sita, reductions of 8.9%, 10.5% and 10.7% were observed, respectively, as compared to 6.5% with Sita alone.

CONCLUSIONS

In this single-dose clinical trial, we provide a proof of concept that addition of low doses of DXM, including 30 mg (sold as over-the-counter medication for cough suppression), to Sita substantially increase postprandial serum insulin concentrations and reduce BG excursions during an OGTT without introducing hypoglycemic events. The trial represents the 'first in man study' showing that DXM increases the BG-lowering effect of a DPP-4 inhibitor and thus warrants long-term clinical trials on a combination of a low dose of DXM with DPP-4 inhibitors or incretins. The latter are also worthwhile, since both drugs seem to protect the insulin-secreting pancreatic beta cells from cell death and might together reduce or even stop diabetes progression (Marquard et al., 2015; Farilla...Perfetti, Endocrinol 2003). Moreover, glutamate-mediated NMDA receptor activation was recently suggested to contribute to

diabetic long-term complications, including diabetic retinopathy, nephropathy and neuropathy (Simo & Hernandez, TEM 2014; Kundu...Sen, Nitric Oxide 2015; Bai...Wang, J Neurol Sci 2014; 341: 68-72), providing yet another incentive for long-term clinical trials.

References

Other information

Registration

The trial is registered at ClinicalTrials.gov, number NCT01936025

Protocol

The protocol can be requested from tim.heise@profil.com.

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Acknowledgments

Author contributions

JM and EL designed the structure of manuscript and figures and wrote the manuscript with input from the other authors. JM generated figures and tables with input from EL and AS. EL suggested to TH to perform a clinical trial on a combination of a low dose of DXM with a DPP-4 inhibitor, while TH suggested the use of sitapliptin. AS, F Sievers, F Schliess, and TH guided the clinical trial whose protocol was written by AS with input from EL, JM, TH, F

Schliess and TM. AF drew a statistical analysis for clinical study design and performed statistical analyses. SW determined the insulin and glucagon concentrations. AW and SO re-evaluated all calculations made.

Competing financial interest

JM, TM and EL declare competing financial interests: These authors pursue a patent application (WO 2013/029762 A1) entitled 'Morphinan-derivatives for treating diabetes and related disorders'.

Figure and Table legends