A systems pharmacology model of SGLT2 and SGLT1 inhibition to understand mechanism and quantification of urinary glucose excretion after treatment with dapagliflozin, canagliflozin and empagliflozin

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EXECUTIVE SUMMARY

• Gliflozins are inhibitors of the sodium-dependent glucose co-transporter 2 (SGLT2) and are widely used in type 2 diabetes (T2D) therapies;
• Given the overwhelming contribution (>80%) of SGLT2 to renal glucose reabsorption (rGR), it has been expected that SGLT2 inhibitors, at sufficient exposures, would reduce rGR by over 80%. However, the clinical observations demonstrated that only 30–50% of inhibition was achieved with dapagliflozin and canagliflozin;
• Quantitative systems pharmacology (QSP) modeling approach was used to explain the mechanism underlying this apparent discrepancy in clinical data.

INTRODUCTION

Under normal conditions, glucose is fully reabsorbed along proximal tubules, and primarily by SGLT2 and SGLT1. Inhibition of this glucose reabsorption process results in plasma glucose lowering, a desirable feature for diabetic patients. Several SGLT2 inhibitors are approved in the USA and in Europe.

SGLT2/1 transporters are located in different segments of proximal tubules and exhibit differential contributions to rGR. Based on *in vitro* experimental data, SGLT2 is believed to be responsible for 80–90% of rGR, and SGLT1 for the remaining 10–20% [1]. Hence, it is expected that SGLT2 inhibitors would reduce rGR by at least 80%. This is, however, in contradiction to clinical observations, whereby only 30–50% glucose reabsoprtion inhibition is achieved with dapa- and canagliflozins [2-4].

OBJECTIVES

- To evaluate the relative SGLT2 *vs*. SGLT1 contributions towards *in vivo* renal glucose reabsorption*;*
- To explain the mechanism underlying the apparent discrepancy in clinical data, using a quantitative systems pharmacology (QSP) modeling approach.

METHODS

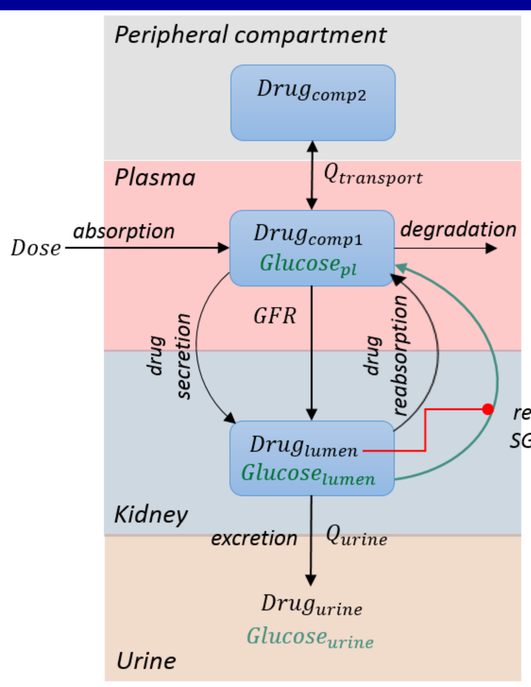


Fig. 1. General model structure

where:
GFR – glomerular filtration rate, 120 ml/min;
Q_{urine} *– urine formation flux;*
$Q_{transport}$ *– transport flux between compartments (only for dapagliflozin);*
$Glucose_{lumen}$ *- glucose concentration in proximal tubules;*
$Drug_{lumen}$ *- concentration of compound in proximal tubules*

The QSP model is described using a system of ordinary differential equations (ODEs). Kinetic processes are described based on a combination of approaches proposed in previous publications [6,7]. The QSP model thus describes:

1. Plasma PK profiles, kidney distribution, and excretion for three gliflozins:
   - dapagliflozin (2-compartment PK model),
   - canagliflozin (1-compartment PK model),
   - empagliflozin (1-compatment PK model);
2. Glucose filtration, reabsorption, and urinary glucose excretion (UGE).

In the model, the drug molecule competes with glucose for SGLT1 and SGLT2, and hence competitively inhibits glucose reabsorption:

$$V_{reabs_{SGLT1,SGLT2}} = \frac{V_{max} * Glucose_{lumen}}{Km * \left(1 + \frac{Drug_{lumen}}{IC50}\right) + Glucose_{lumen}}$$

V_{max} $-$ *maximal reabsorption rate capacity of particular transporter;*
V_{reabs} $-$ *reacorption rate for SGLT1 or SGLT2;*
Km $-$ *glucose affinity for each of SGLT1/SGLT2, taken from the literature* [8].

Total SGLT2 and SGLT1 reabsorption capacity in the model did not exceed the physiological threshold of maximum glucose reabsorption (140 mmol/h):

$$Vmax_{reabs\_SGLT1} = 140 - Vmax_{reabs\_SGLT2}$$

Available data from clinical studies of dapa-, cana- and empagliflozin [2-5] were used to estimate parameter values.

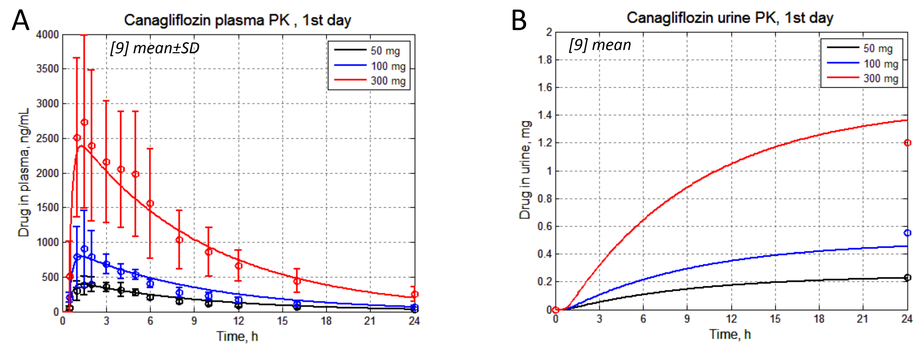
The modeling work was performed using the IQM software by IntiQuan (derived from the SBTOOLBOX2 software - http://www.intiquan.com/).

RESULTS

Pharmacokinetic (PK) of gliflozins

PK parameters for each of the gliflozins were estimated against experimental data (drug plasma profiles after various dosing regimens, and 24–hour urinary excretion profiles).

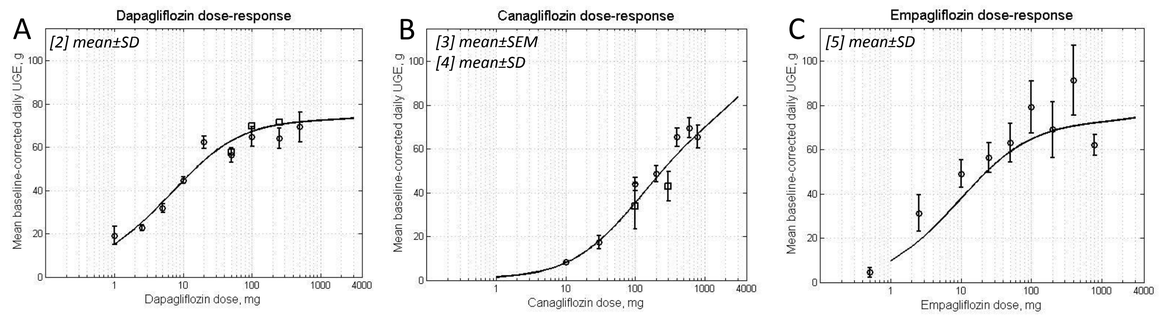
Fig. 2. Example of drug PK, canagliflozin. A. Plasma concentration; B. 24-hour drug amount in urine



Urinary glucose excretion after treatment with gliflozins

The QSP model of SGLT1/2 inhibition and UGE quantification adequately described the experimental 24-hour UGE data, following treatment with various dosages of dapa-, cana- and empagliflozin in healthy subjects (Fig. 3).

Fig. 3. 24-hour UGE after treatment with dapagliflozin (A), canagliflozin (B), empagliflozin (C)

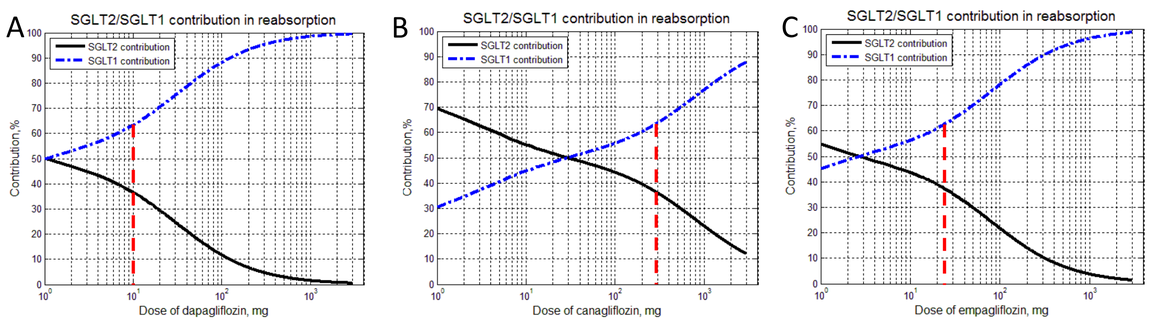


Maximum contribution of SGLT2 ($Vmax_{reabs\_SGLT2}$) and SGLT1 ($Vmax_{reabs\_SGLT1}$) to the total renal glucose reabsorption under conditions of saturation with glucose were fitted to 87% and 13%, respectively, which correlates closely with *in vitro* experimental data on transporter contributions (80-90% and 10-20%, respectively) [1].

SGLT2 *vs*. SGLT1 contributions to the *in vivo* reabsorption rate

Following gliflozin treatment, contributions from each of the transporters change depending on the dose of the inhibitor used and has a 35% value for the treatment with the registered doses for all considered drugs.

Fig. 4 Relative transporter contributions towards reabsorption, for treatments with dapagliflozin (A), canagliflozin (B), empagliflozin (C).



- - - Particular drug registered doses: 10 mg for dapagliflozin, 300 mg for canagliflozin, 25 mg for empagliflozin

High dosages of drugs lead to strong inhibition of SGLT2, but not of SGLT1, because the IC_{50} for SGLT1 is several times higher *vs*. the IC_{50} for SGLT2. Therefore, contributions of SGLT1 towards the overall reabsorption process increases with dosages of gliflozins.

- Observed UGE levels are dependent on corresponding IC_{50} values for SGLT2 and SGLT1, as well as lumen concentrations for each of the drugs;
- The maximum contribution of SGLT2 to rGR was estimated at 87%.
- The contribution of SGLT2 to rGR without drug administration and healthy subjects with normal renal function was predicted to be around 77%; the contribution of SGLT2 to rGR is about 35% given treatment with the three gliflozins at registered doses.

CONCLUSIONS

The QSP model of SGLT2/SGLT1 inhibition allowed us to describe the relationship between UGE and rGR processes and estimate relative contributions of transporters towards the total rGR rate.

We found that SGLT1 contribution towards total glucose reabsorption increases with dosages of gliflozins, which could be a compensatory mechanism underlying the apparent discrepancy in UGE levels, as observed across gliflozin compounds.

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ADDITIONAL INFORMATION

We would like to thank our colleague Kirill Peskov for his valuable contribution to the modelling discussions.

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