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Drug-drug interactions with SGLT-2 inhibitors, new oral glucose-lowering agents for the management of type 2 diabetes

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SUMMARY

Inhibitors of sodium-glucose cotransporters type 2 (SGLT2) reduce hyperglycaemia by decreasing renal glucose threshold and thereby increasing urinary glucose excretion. They are proposed as a novel approach for the management of type 2 diabetes mellitus. They have proven their efficacy in reducing glycated haemoglobin, without inducing hypoglycaemia, as monotherapy or in combination with various other glucose-lowering agents, with the add-on value of promoting some weight loss and lowering arterial blood pressure. As they may be used concomitantly with many other drugs, we review the potential drug-drug interactions regarding the three leaders in the class (dapagliglozin, canagliflozin and empagliflozin). Most of the available studies were performed in healthy volunteers and have assessed the pharmacokinetic interferences with a single administration of the SGLT2 inhibitor. The exposure (assessed by peak plasma concentrations - C_{max} - and area under the concentration-time curve – AUC -) to each SGLT2 inhibitor tested was not significantly influenced by the

concomitant administration of other glucose lowering agents or cardiovascular agents commonly used in patients with type 2 diabetes. Reciprocally, these medications did not influence the pharmacokinetic parameters of dapagliflozin, canagliflozin or empagliflozin. Some modest changes were not considered as clinically relevant. However, drugs which could specifically interfere with the metabolic pathways of SGLT2 inhibitors (rifampin, inhibitors or inducers of uridine diphosphate-glucuronosyltransferase – UGT -) may result in significant changes in the exposure of SGLT2 inhibitors, as shown for dapagliflozin and canagliflozin. Potential drug-drug interactions in patients with type 2 diabetes receiving a chronic treatment with a SGLT2 inhibitor deserve further attention, especially in the numerous individuals treated with several medications or in more fragile patients with hepatic and/or renal impairment.

Key-words : Canagliflozin – Dapagliflozin – Empagliflozin – Glucose-lowering therapy – Pharmacokinetics – Drug-drug interaction – Type 2 diabetes mellitus

1. Introduction

The incidence of type 2 diabetes mellitus (T2DM) is increasing worldwide. Because this chronic disease leads to numerous medical complications and represents a huge burden for both patients and society, extensive research is still ongoing to develop new pharmacological approaches to tackle T2DM. The oral therapy of T2DM was dominated during decades by only two pharmacological classes, sulphonylureas and biguanides^[1, 2]. The risk of potential drug-drug interactions (DDIs) was rather limited at that time even if DDI with sulphonylureas (mainly glibenclamide) leading to severe hypoglycaemia have been reported^[3]. Alpha-glucosidase inhibitors were the next available antidiabetic agents and act directly in the gut. Acarbose was shown to slightly reduce the bioavailability of metformin in healthy volunteers^[4] although DDIs with alpha-glucosidase inhibitors are probably not clinically relevant. Numerous other oral glucose-lowering agents are now available, which targets either insulin secretion (insulin-secreting agents : besides sulphonylureas, glinides and, more recently, incretin-based therapies called gliptins) or insulin action (insulin sensitizers : besides metformin, thiazolidinediones or glitazones). Thus, numerous patients are currently treated with various combinations of glucose-lowering agents^[5, 6]. Furthermore, to reduce the risk of cardiovascular complications, a global approach is recommended since many years so that most patients with T2DM also receive various antihypertensive medications, lipid-lowering drugs and antiplatelet agents^[7, 8]. Finally, patients with T2DM are more prone to have cardiovascular diseases^[7] or various infections and thereby may also receive in the long run or transiently several other medications, which could potentially interfere with their glucose-lowering agents. Because most T2DM patients receive concomitantly numerous medications, the issue of DDIs is becoming increasingly important in diabetes^[9]. DDIs may have clinical implications and expose the diabetic patient to severe complications as it was reported with the occurrence of severe hypoglycaemia in patients receiving sulphonylureas (glibenclamide, glimepiride, glipizide), presumably due to CYP2C9-mediated DDIs^[10].

Since our updated general overview on DDI of clinical importance with antihyperglycaemic agents published in 2005^[9], several reviews more specifically focused on one particular class of glucose-lowering agents : thiazolidinediones (rosiglitazone, pioglitazone)^[11], glinides (repaglinide, nateglinide)^[12], inhibitors of dipeptidyl peptidase-4 (DPP-4) (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin)^[13] and agonists of the glucagon-like peptide-1 (exenatide, liraglutide, lixisenatide)^[14].

The existing therapeutic classes of oral antidiabetic drugs are not adequately effective in maintaining long-term glycaemic control in most patients with T2DM, even when used in

combination^[5], and there remains a medical need for improving pharmacological therapy of T2DM^[15]. Inhibitors of sodium-glucose cotransporters type 2 (SGLT2) are new glucose-lowering agents, which specifically target the kidney by blocking the reabsorption of filtered glucose, thus leading to glucosuria^[16, 17]. This mechanism of action holds potential promise for patients with T2DM not only in terms of improvements in glycaemic control, but also considering the potential benefits of weight loss and arterial blood pressure reduction^[16, 17]. SGLT2 inhibitors may be used as monotherapy in diet-treated patients or in combination with any other glucose-lowering agent^[18]. PK characteristics of SGLT2 inhibitors show an excellent oral bioavailability, a rather long half-life allowing once daily administration, a low accumulation index, no active metabolites and a negligible renal clearance (Table 1)^[19]. To our knowledge, there is no review analyzing DDIs with SGLT2 inhibitors.

The aim of this review is to provide an extensive analysis of potential DDIs of the recently launched SGLT-2 inhibitors - dapagliflozin^[20, 21] and canagliflozin^[22, 23] – and in late phase of clinical development - empagliflozin^[24].

2. Literature search

To identify relevant studies, an extensive literature search in MEDLINE was performed from 2008 to October 2013, with the following MESH terms : SGLT2 inhibitor, canagliflozin, dapagliflozin, or empagliflozin combined with “drug-drug interaction” or “drug interaction”. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

DDI can be evaluated in two ways : either the effect of a second drug on the pharmacokinetics (PK) of the SGLT2 inhibitor (Table 2) or the effect of the SGLT2 inhibitor on the PK of the second drug (Table 3). Whenever available, data were expressed as the ratio of adjusted geometric mean point estimates (GMR) with 90% confidence interval (CI). We will analyze successively the DDIs of SGLT2 inhibitors with other glucose-lowering agents, with cardiovascular medications commonly used in patients with T2DM and with various drugs of special interest because they have a narrow therapeutic margin or they may interfere with the metabolic pathways of SGLT2 inhibitors. Most of the data found in the literature were obtained in healthy volunteers after a single administration of the SGLT2 inhibitor. Caution is thus recommended in the interpretation of the available data, which could not be automatically extrapolated to patients with T2DM, especially when comorbidities are present such as chronic kidney disease (CKD)^[19, 25] or hepatic impairment^[19].

3. PK/PD characteristics of SGLT2 inhibitors

The main PK characteristics of the three SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin), which were essentially derived from studies in healthy volunteers, are summarized in Table 1. No clinically relevant differences were observed in either compound exposure with respect to age, race, sex, body weight, food, or presence of T2DM. Pharmacodynamic (PD) changes, assessed by urinary glucose excretion (UGE), are dependent on plasma glucose level and renal function (estimated by glomerular filtration rate or GFR). Decreases in UGE were observed due to the lower filtered load (plasma glucose \times GFR) in healthy volunteers compared to subjects with T2DM as well as in patients with moderate to severe CKD compared with patients with normal renal function^[19, 25]. In patients with T2DM and normal renal function, UGE increased according to the dose of SGLT2 given. However, for the doses used in clinical practice, no major changes in glucose-lowering efficacy should be observed even if DDIs result in changing the plasma concentrations of dapagliflozin^[20, 21], canagliflozin^[22, 23] or empagliflozin^[24, 26] by a factor two.

3.1. Dapagliflozin

Clinical PK and PD of dapagliflozin have been recently extensively reviewed^[21]. Orally administered dapagliflozin is rapidly absorbed generally achieving peak plasma concentrations (t_{max}) within 1-2 h. Dose-proportional systemic exposure to dapagliflozin has been observed over a wide dose range (0.1-500 mg) with an oral bioavailability of 78 %. Dapagliflozin has extensive extravascular distribution as shown by a mean volume of distribution averaging 118 L (Table 1). Dapagliflozin metabolism occurs predominantly in the liver and kidneys by uridine diphosphate-glucuronosyltransferase-1A9 (UGT1A9) to the major metabolite dapagliflozin 3-O-glucuronide (this metabolite is not an SGLT2 inhibitor at clinically relevant exposures). Dapagliflozin is not appreciably cleared by renal excretion (<2 % of dose is recovered in urine as parent), in contrast to its major metabolite that is mainly eliminated via renal excretion. Based on the PK characteristics of dapagliflozin, there is a potential for clinically relevant interactions with inhibitors and inducers of UGT1A9. However, potent inhibitors of UGT1A9 seem to be rare. One study investigated the interaction between dapagliflozin and mefenamic acid, an UGT1A9 inhibitor (see below).

3.2. Canagliflozin

The PD/PD and metabolism of canagliflozin have also been recently reviewed^[22, 23]. After oral administration canagliflozin is rapidly absorbed in a dose-dependent manner across a dose range of 50–300 mg. The mean absolute oral bioavailability is approximately 65 %. After canagliflozin 100 or 300 mg, median t_{max} values occurred within 1–2 h, with steady-state levels attained after 4–5 days following multiple once daily doses. Canagliflozin does not exhibit time-dependent PK and, following multiple 100 and 300 mg doses, accumulates in the plasma up to 36 %. The drug is extensively (99 %) bound to plasma proteins, mainly albumin (Table 1). Canagliflozin is mainly metabolized via glucuronidation by UGT1A9 and UGT2B4 to two inactive O-glucuronide metabolites. Such UGT enzymes can be inhibited or induced and have the potential to change canagliflozin systemic exposure. Canagliflozin has only minor (≈ 7 % in humans) metabolism by cytochrome P450 (CYP) 3A4. In *in vitro* studies, canagliflozin did not induce or inhibit most CYP enzyme expression, although it weakly inhibited CYP2B6, CYP2C8, CYP2C9 and CYP3A4^[22]. Whether these effects might be relevant *in vivo* and have clinical consequences remains unknown.

3.3. Empagliflozin

Single oral doses of empagliflozin were rapidly absorbed, reaching peak levels after 1.0–2.0 hours (Table 1). Increases in empagliflozin exposure were roughly dose-proportional and a dose-dependent increase in UGE was observed for empagliflozin doses up to 100 mg^[26]. PK/PD characteristics of empagliflozin have been recently reviewed in healthy volunteers and patients with T2DM, including patients with CKD or hepatic impairment^[24]. However, description of absorption, distribution, metabolism, and excretion (ADME) characteristics of empagliflozin in humans has not been extensively reported yet^[27].

4. Drug-drug interactions with other glucose-lowering agents

Because of their mode of action, SGLT-2 inhibitors can be combined with any other glucose-lowering agent^[18]. PD investigations and clinical studies have shown complementary efficacy in reducing fasting and postprandial glucose and glycated haemoglobin (HbA_{1c}) levels.

4.1. Dapagliflozin

PK DDI studies in healthy volunteers showed that dapagliflozin can be co-administered with pioglitazone, metformin, glimepiride or sitagliptin without dose adjustment of either drug^[28]. The other glucose-lowering agents did not impact PK of dapagliflozin (only

a slight - + 8% -greater exposure to dapagliflozin after coadministration of sitagliptin was observed, without any clinically relevance) (Table 1). Reciprocally, dapagliflozin did not significantly influence the PK parameters of the other glucose-lowering agents (only a trend for a slightly greater exposure to glimepiride was detected) (Table 2). The addition of dapagliflozin in patients insufficiently controlled with glimepiride resulted in significant reduction in HbA_{1c} with only a slightly increased risk of hypoglycaemia^[29]. A Japanese study demonstrated that voglibose, an alpha-glucosidase inhibitor, does not modify the PK of dapagliflozin^[30]. Several clinical studies have confirmed that dapagliflozin is effective and safe when combined with other glucose-lowering agents for the management of T2DM^[20].

4.2. Canagliflozin

Rather few data are available regarding DDIs with canagliflozin^[31] and they are only published as congress abstracts^[32]. Metformin slightly increased exposure to canagliflozin (C_{max} : + 5%; AUC : + 10%) (Table 1) whereas canagliflozin did not modify the exposure to metformin (Table 2). However, these changes were rather modest without any clinical relevance^[32]. No PK interferences were reported between canagliflozin and glyburide (glibenclamide) (Table 2)^[32].

4.3. Empagliflozin

Empagliflozin has been tested in single dose studies when co-administered with various other glucose-lowering agents, metformin^[33], glimepiride^[34], sitagliptin^[35], linagliptin^[36]. Glimepiride slightly decreased exposure to empagliflozin whereas sitagliptin modestly increased it (Table 1). However, these changes are too small for being considered as clinically relevant. Empagliflozin did not significantly modify exposure to other glucose-lowering agents tested so far (Table 2).

5. Drug-drug interactions with cardiovascular agents

Because of the high cardiovascular risk of patients with T2DM^[7], it is important to assess the potential interferences with other cardiovascular drugs commonly prescribed in those patients^[37].

5.1. Dapagliflozin

Co-administration of dapagliflozin was evaluated with simvastatin, valsartan, warfarin, or digoxin in healthy volunteers^[38]. Simvastatin and valsartan did not influence the exposure to dapagliflozin (Table 1). Dapagliflozin 20 mg was associated with modest

increases in the exposure to simvastatin (GMR : 1.19; 90% CI : 1.01-1.40) and simvastatin acid (GMR : 1.30; 1.15-1.47), but these changes were considered as not clinically meaningful. A mild increase in the exposure to R-warfarin and S-warfarin was also detected when warfarin was prescribed with dapagliflozin (Table 2), without any change in the International Normalized Ratio (INR : GMR : 1.007; 90% CI : 0.989-1.025)^[38]. No other meaningful DDIs were detected, including changes in digoxin levels after dapagliflozin administration^[38] (Table 2).

5.2. Canagliflozin

No clinically relevant PK interferences were reported between canagliflozin and simvastatin or hydrochlorothiazide (Table 1, Table 2)^[31]. Of potential interest, canagliflozin significantly increased the exposure to digoxin (C_{max} : + 36%; AUC : + 20%) (Table 2)^[39]. Therefore, patients taking canagliflozin with concomitant digoxin should be monitored appropriately regarding plasma digoxin concentrations. In contrast, no significant changes in exposure to warfarin and no change in INR were noticed after canagliflozin administration (Table 2)^[39].

5.3. Empagliflozin

DDI studies in healthy volunteers showed no clinically significant interactions between empagliflozin and warfarin^[40], simvastatin^[41], or other cardiovascular compounds (verapamil, ramipril, and digoxin)^[42]. The lack of DDIs between verapamil and empagliflozin indicates there is no relevant effect of P-glycoprotein inhibition on the PK of empagliflozin. Another study evaluated empagliflozin combined with diuretics such as hydrochlorothiazide and torasemide in patients with T2DM^[43]. In the latter study, a slight increase in AUC of empagliflozin was observed with hydrochlorothiazide (+7.1%) and with torasemide (+ 7.8%) (Table 1). These modest changes should not have clinical consequences.

6. Drug-drug interactions with other medications of interest

Drugs of special interest should also be tested because they may interfere with a common metabolic pathway with SGLT-2 inhibitors (i.e. rifampin, mefenamic acid) or because they may have a low therapeutic index (contraceptive pill).

6.1. Dapagliflozin

As dapagliflozin is primarily metabolized via the UGT1A9 pathway to its major inactive metabolite dapagliflozin 3-*O*-glucuronide (D3OG), the potential for DDIs between dapagliflozin and two potential UGT1A9 modulators was evaluated : rifampin, a pleiotropic drug-metabolizing enzyme inducer, and mefenamic acid, a strong UGT1A9 inhibitor. Significant changes in dapagliflozin exposure were seen with rifampin (a significant decrease of AUC : - 22%) and with mefenamic acid (a significant increase of AUC : + 51%) (Table 1). However, only minor changes in UGE were detected, none of which being considered clinically relevant^[44].

6.2. Canagliflozin

No clinically relevant PK interferences were reported between canagliflozin and an oral contraceptive containing ethinyl estradiol and levonorgestrel^[45] (Table 1, Table 2).

However, GMRs of key PK parameters of canagliflozin were significantly reduced after rifampin 600 mg once daily for 8 days : C_{max} : - 28% and AUC : - 51 % (Table 1)^[31]. This decrease in exposure to canagliflozin may slightly decrease efficacy. Rifampin is a nonselective inducer of several UGT enzymes, including UGT1A9 and UGT2B4. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be coadministered with canagliflozin, advice is given to consider increasing the dose to 300 mg once daily if patients are currently tolerating canagliflozin 100 mg once daily, have an estimated GFR greater than 60 mL/min/1.73 m², and require additional glycaemic control^[31]. Otherwise, alternative glucose-lowering agents should be considered.

Finally, exposure to canagliflozin was modestly but significantly increased by cyclosporine (AUC : +23 %) and by probenecid (AUC : + 21%)^[31] (Table 1). Considering the results obtained with ascending doses of canagliflozin in patients with T2DM^[46], these modest changes should not have clinically relevant implications.

6.3. Empagliflozin

DDI studies showed no clinically significant interactions between empagliflozin and the oral contraceptive ethinylestradiol/levonorgestrel (Table 2)^[47].

7. Clinical impact

The metabolic pathways of SGLT2 inhibitors expose them to a low risk of clinically relevant PK DDIs. This is important because most patients with T2DM must be treated with many medications, not only for controlling blood glucose but also for managing other risk

factors (including hypertension and dyslipidaemia) and treating various comorbidities (coronary artery disease, congestive heart failure, etc).

Several studies have demonstrated that the effects of SGLT2 inhibitors on UGE is reduced when GFR is decreasing^[19, 25]. Specific PK studies have shown heterogeneous results in patients with various degrees of CKD^[19]: according to reported changes in systemic exposure, the daily dose of dapagliflozin^[48] or empagliflozin^[49] should not be reduced in patients with moderate CKD whereas the maximum dose recommended for canagliflozin is 100 mg instead of 300 mg^[50, 51]. Even if canagliflozin has been shown to be efficacious and safe in diabetic patients with mild to moderate CKD^[52], all drugs that may interfere with renal function, by decreasing GFR (for instance, non steroidal anti-inflammatory drugs), may exert PD (rather than PK) DDIs and reduce the glucose-lowering effects of SGLT2 inhibitors in fragile patients. In clinical practice, renal function should be regularly monitored in diabetic patients treated with SGLT2 inhibitors, especially in patients with mild/moderate CKD, and all agents that may interfere with kidney function should be used with caution^[25]. Finally, dose adjustment and special caution may be recommended in patients on loop diuretics, especially in elderly people, if there are concerns or symptoms of volume-related side effects^[23]. The observation that there were only negligible PK interactions between canagliflozin and hydrochlorothiazide^[31] or between empagliflozin and hydrochlorothiazide or torasemide, a loop diuretic,^[43] in patients with T2DM does not mean that a clinically relevant PD interaction could be excluded at least in some more fragile patients.

8. Conclusion

All available studies investigating potential DDIs between SGLT2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) and other drugs commonly used in patients with T2DM provide reassuring results with no clinically relevant PK interferences detected when combined with other glucose-lowering agents or cardiovascular drugs. However, these data should be interpreted with some caution because they were obtained in healthy volunteers and in most instances after a single acute administration of the SGLT2 inhibitor. Nevertheless, large phase 3 clinical trials lasting up to 1-2 years showed no clinically relevant safety issues when the SGLT2 inhibitors are prescribed with other glucose-lowering agents and several cardiovascular drugs. However, when agents selectively acting on pathways playing a role in the metabolism of SGLT2 inhibitors (UGT inducers or inhibitors) are prescribed, larger changes in exposure to dapagliflozin and canagliflozin may occur, which

might have clinical consequences. Further studies are required to investigate more extensively potential DDIs in patients with T2DM chronically treated with a SGLT2 inhibitor.

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Figure 1 : Chemical structures of dapagliflozin, canagliflozin and empagliflozin.

Table 1 : Main pharmacokinetic characteristics of dapagliflozin, canagliflozin and empagliflozin.

Data are expressed as approximate mean values.

Parameter	Dapagliflozin ^[19-21]	Canagliflozin ^[19, 22, 23]	Empagliflozin ^[19, 24, 26]
Dose (single) (mg)	5/10	100/300	10/25
Oral bioavailability (%)	78	≈65	Not available
T _{max} (h)	1-2	1-2	1-2
C _{max} ng/ml	94/158	1069/2939	102/227 (*)
AUC ng.h/ml	324/628	6871/20972	786/1725 (*)
Plasma protein binding (%)	91	99	Not available
Elimination t _{1/2} (h)	12.2/12.9	10.6/13.1	13.1/10.2
V _{ss} (iv administration) (L)	118	119	Not available
Mean systemic clearance (iv administration) (mL/min)	207	192	Not available
Renal clearance (mL/min)	≈ 5	≈ 1-2	≈ 40
Metabolism	Extensive glucuronidation to inactive conjugates	O-glucuronidation to M7 (major metabolite) and M5 (minor metabolite)	ADME not yet reported
Elimination	75% in urine (parent drug and inactive metabolites) and 21% in faeces	Biliary excretion (60%) and urine (32%) <1% unchanged in urine	11-19% unchanged in urine
Main metabolizing enzyme	UGT1A9 (kidney and liver)		ADME not yet reported
CYP metabolism (substrate/inhibitor/inducer)	No	Minimal (7% CYP3A4) Weak inhibition of CYP2B6, CYP2C8,	ADME not yet reported

		CYP2C9, and CYP3A4	
P-gp substrate	Weak	Weak inhibitor	ADME not yet reported
OAT3 substrate	Main inactive metabolite dapagliflozin 3-O-glucuronide		
Dose-proportionality	Yes (0.1-500 mg)	Yes (50-300 mg)	Yes (0.5-800 mg)
Time-dependency (repeated doses)	No	No	No

(*) Units transformed from nmol/l to ng/ml (1 nmol/l = 0.45045 ng/ml)

T_{max} : time to reach maximum plasma concentration. C_{max} : maximum plasma concentration. AUC : area under the concentration-time curve. V_{ss} : distribution volume at steady-state. Iv : intravenous. P-gp : P-glycoprotein. OAT3 : organic anion transporters type 3. ADME : drug absorption, distribution, metabolism, and excretion

Table 2 : Effect of a second drug selected because of special interest on the PK characteristics of the SGLT-2 inhibitor. Results are expressed as the ratio of adjusted geometric mean point estimates (90% CI).

DRUGS	EXPOSURE	DAPAGLIFLOZIN	CANAGLIFLOZIN	EMPAGLIFOZIN
Oral antidiabetic agents				
Metformin	C _{max}	0.93 (0.85-1.02) [28]	1.05 (0.96-1.16) [31]	1.01 (0.89-1.14) [33]
	AUC	1.01 (0.95-1.06)	1.10 (1.05-1.15)	0.97 (0.92-1.02)
Glimepiride	C _{max}	1.01 (0.92-1.10) [28]	NA	0.96 (0.88-1.04) [34]
	AUC	1.00 (0.97-1.02)	NA	0.95 (0.92-0.99)
Glyburide/ Glibenclamide	C _{max}	NA	NA	NA
	AUC	NA	NA	NA
Pioglitazone	C _{max}	1.09 (1.00-1.18) [28]	NA	NA
	AUC	1.03 (0.98-1.07)	NA	NA
Sitagliptin	C _{max}	0.96 (0.88-1.05) [28]	NA	1.08 (0.97-1.19) [35]
	AUC	1.08 (1.03-1.13)	NA	1.10 (1.04-1.17)
Linagliptin	C _{max}	NA	NA	0.88 (0.79-0.99) [36]
	AUC	NA	NA	1.02 (0.97-1.07)
Voglibose	C _{max}	1.04 (0.90-1.20) [30]	NA	NA
	AUC	1.01 (0.95-1.07)	NA	NA
Cardiovascular medications				
Simvastatin	C _{max}	0.98 (0.89-1.08) [38]	NA	1.10 (0.97-1.24) [41]
	AUC	0.98 (0.95-1.01)	NA	1.02 (0.99-1.05)
Valsartan	C _{max}	0.88 (0.80-0.98) [38]	NA	NA
	AUC	1.02 (1.00-1.05)	NA	NA
Ramipril	C _{max}	NA	NA	1.05 (0.98-1.12) [42]
	AUC	NA	NA	0.97 (0.93-1.00)
Hydrochlorothiazide	C _{max}	NA	1.15 (1.06-1.25) [31]	1.03 (0.89-1.19) [43]
	AUC	NA	1.12 (1.08-1.17)	1.07 (0.97-1.18)
Torasemide	C _{max}	NA	NA	1.08 (0.98-1.18) [43]
	AUC	NA	NA	1.08 (1.00-1.17)
Verapamil	C _{max}	NA	NA	0.92 (0.85-0.99) [42]
	AUC	NA	NA	1.03 (0.99-1.07)
Warfarin	C _{max}	NA	NA	1.01 (0.90-1.13) [40]

	AUC	NA	NA	1.01 (0.97-1.05)
Drugs of special interest				
Ethinylestradiol/ Levonorgestrel	C _{max}	NA	0.92 (0.84-0.99) [45]	NA
	AUC	NA	0.91 (0.88-0.94)	NA
Rifampin	C _{max}	0.93 (0.78-1.11) [44]	0.72 (0.61-0.84) [31]	NA
	AUC	0.78 (0.73-0.83)	0.49 (0.44-0.54)	NA
Mefenamic acid	C _{max}	1.13 (1.03-1.24) [44]	NA	NA
	AUC	1.51 (1.44-1.58)	NA	NA
Cyclosporin	C _{max}	NA	1.01 (0.91-1.11) [31]	NA
	AUC	NA	1.23 (1.19-1.27)	NA
Probenecid	C _{max}	NA	1.13 (1.00-1.28) [31]	NA
	AUC	NA	1.21 (1.16-1.25)	NA

C_{max} : maximum plasma concentration. AUC : area under the concentration-time curve. NA : not available.

Table 3 : Effect of the SGLT2 inhibitor on the PK characteristics of a second drug selected because of special interest. Results are expressed as the ratio of adjusted geometric mean point estimates (90% CI).

DRUGS	EXPOSURE	DAPAGLIFLOZIN	CANAGLIFLOZIN	EMPAGLIFOZIN
Oral antidiabetic drugs				
Metformin	C _{max}	0.95 (0.87-1.05) [28]	0.86 (0.73-1.01) ^[32]	1.04 (0.97-1.11) [33]
	AUC	1.00 (0.94-1.07)	0.97 (0.82-1.14)	1.01 (0.96-1.06)
Glimepiride	C _{max}	1.04 (0.91-1.20) [28]	NA	1.04 (0.90-1.21) [34]
	AUC	1.13 (0.99-1.29)	NA	0.93 (0.86-1.01)
Glyburide/ Glibenclamide	C _{max}	NA	0.93 (0.85-1.01) [32]	NA
	AUC	NA	1.02 (0.98-1.07)	NA
Pioglitazone	C _{max}	0.93 (0.75-1.15) [28]	NA	NA
	AUC	0.97 (0.87-1.08)	NA	NA
Sitagliptin	C _{max}	0.89 (0.81-0.97) [28]	NA	1.09 (1.01-1.17) [35]
	AUC	1.01 (0.98-1.04)	NA	1.03 (0.99-1.07)
Linagliptin	C _{max}	NA	NA	1.01 (0.87-1.19) [36]
	AUC	NA	NA	1.03 (0.96-1.11)
Cardiovascular medications				
Simvastatin	C _{max}	0.94 (0.82-1.07) [38]	1.09 (0.91-1.31) [31]	0.97 (0.76-1.24) [41]
	AUC	1.19 (1.01-1.40)	1.12 (0.94-1.33)	1.01 (0.80-1.28)
Valsartan	C _{max}	0.94 (0.76-1.16) [38]	NA	NA
	AUC	1.06 (0.87-1.30)	NA	NA
Ramipril	C _{max}	NA	NA	1.04 (0.90-1.20) [42]
	AUC	NA	NA	1.08 (1.05-1.16)
Hydrochlorothiazide	C _{max}	NA	0.94 (0.87-1.01) [31]	1.02 (0.89-1.17) [43]
	AUC	NA	0.99 (0.95-1.04)	0.96 (0.89-1.04)
Torasemide	C _{max}	NA	NA	1.04 (0.94-1.16) [43]
	AUC	NA	NA	1.01 (0.99-1.04)
Digoxin	C _{max}	0.99 (0.84-1.16) [38]	1.36 (1.21-1.53) [39]	1.14 (0.99-1.31) [42]
	AUC	1.00 (0.86-1.17)	1.20 (1.12-1.28)	1.06 (0.97-1.16)
R-Warfarin	C _{max}	1.06 (1.00-1.15) [38]	1.03 (0.94-1.13) [39]	0.98 (0.91-1.05) [40]
S-Warfarin	AUC	1.08 (1.03-1.12)	1.01 (0.96-1.06) [39]	0.99 (0.95-1.02)

	C _{max}	1.03 (0.99-1.12) [38]	1.01 (0.90-1.13)	0.99 (0.92-1.07) [40]
	AUC	1.07 (1.01-1.14)	1.06 (1.00-1.12)	0.96 (0.93-0.98)
Drugs of special interest				
Ethinylestradiol	C _{max}	NA	1.22 (1.10-1.35) [45]	0.99 (0.93-1.05) [47]
Levonorgestrel	AUC	NA	1.07 (0.99-1.15)	1.03 (0.98-1.08)
	C _{max}	NA	1.22 (1.11-1.35) [45]	1.06 (1.00-1.13) [47]
	AUC	NA	1.06 (1.00-1.13)	1.02 (0.99-1.06)
Cyclosporin	C _{max}	NA	NA	NA
	AUC	NA	NA	NA
Acetaminophen	C _{max}	NA	1.00 (0.92-1.09) [31]	NA
	AUC	NA	1.06 (0.98-1.14)	NA

C_{max} : maximum plasma concentration. AUC : area under the concentration-time curve. NA : not available.

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