

Review

Oral glucose lowering drugs in type 2 diabetic patients with chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) represents a challenge in the treatment of type 2 diabetic patients. Renal impairment may affect drug clearance and other pharmacokinetic processes which can increase toxicity and drug to drug interactions or cause ineffective therapy. There are many oral glucose lowering drugs available for the treatment of type 2 diabetes mellitus (T2DM) with different mechanisms of action and different pharmacokinetic profiles. While all classes may be used in patients with mild renal impairment, therapeutic options for patients with moderate to severe CKD are still limited. This review focuses on the pharmacokinetics, metabolism, and safety of oral glucose lowering drugs in patients with T2DM and CKD.

Key words: Chronic kidney disease, Oral glucose lowering drugs, Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders worldwide with its prevalence being unprecedented in both developed and developing countries.¹ T2DM is the leading cause of end-stage renal disease (ESRD) all over the world, while patients with CKD of other etiologies may also develop T2DM.² Management of T2DM in patients with renal impairment is a complex process that requires a comprehensive approach. Clinicians must be aware that as renal function worsens, abnormalities in glucose homeostasis develop, affecting secretion,

clearance, and peripheral tissue sensitivity to insulin.³ Several factors contribute to hyperglycemia, namely decreased insulin production and insulin resistance.

Accumulation of uremic toxins (which blunt ability to suppress hepatic gluconeogenesis), chronic inflammation, excess visceral fat, oxidative stress, and metabolic acidosis can all affect the insulin signaling pathway and induce insulin resistance. On the other hand, hypoglycemia may also develop in patients with advanced CKD due to accumulation of uremic toxins, which lead to lower hepatic and renal insulin degradation, and also as a result of decreased renal gluconeogenesis, uremic malnutrition, and deficient catecholamine release. Assessment of glucose control in patients with progressive kidney disease by measuring HbA_{1c} may also be a challenge. Falsely increased values may occur as a result of carbamyla-

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Received 03-10-2013, Accepted 21-11-2013

tion of the hemoglobin and acidosis. Meanwhile, reduced red blood cell lifespan, transfusions, and hemolysis may contribute to falsely reduced HbA_{1c} values. Nevertheless, HbA_{1c} remains the best clinical marker of long-term glycemic control, particularly if combined with self-monitoring of blood glucose.⁴ Glycated albumin, as an alternative, reflects glycemic control over a 2-week period and may be of greater value for predicting clinical outcomes in patients with advanced CKD. Besides considering the particularities of treating T2DM in patients with CKD, clinicians should also be aware of the therapeutic options. Many drugs are available for treatment of T2DM, namely biguanides, sulfonylureas (SUs), meglitinide analogues, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, dipeptidylpeptidase-4 (DPP-4) inhibitors, dopamine receptor agonists, and in the near future sodium-glucose co-transporter (SGLTs) inhibitors and G-protein coupled receptor 40 agonists (GPR 40). Although all drugs can be used in patients with mild renal impairment,^{4,5} therapeutic options for patients with moderate to severe CKD or with ESRD are limited, since drug or metabolite accumulation may occur due to a reduced glomerular filtration rate (GFR) resulting in increasing side effects. In this case, some drugs are not recommended, while others can be used with dose adjustment. This paper reviews the pharmacokinetics, metabolism, and safety of oral glucose lowering drugs in patients with T2DM and CKD.

ORAL HYPOGLYCEMIC DRUGS

Biguanides

Metformin, the only available biguanide, is the first line drug in T2DM therapy.⁵ It acts mainly by decreasing hepatic glucose production, but also increases peripheral glucose uptake and reduces intestinal glucose production, improving glucose tolerance and lowering fasting and postprandial plasma glucose.⁶ It is predominantly absorbed in the small intestine and its peak plasma concentrations are attained 3 hours after intake. Metformin does not bind to plasma proteins and it is excreted unchanged in urine. The elimination half-life ($t_{1/2}$) is approximately 5 hours.

Metformin does not cause hypoglycemia nor weight gain⁵ and has been shown to reduce long-

term diabetes complications, although the effect on macrovascular disease is controversial.⁷ In a meta-analysis of 35 randomized clinical trials, including 7,171 and 11,301 participants treated with metformin and comparator, respectively, metformin was associated with a reduction of cardiovascular risk when compared with placebo or no therapy, whereas its effect disappeared when active-comparator trials were included.⁸ The authors speculated that the cardiovascular protection conferred is related to the improvement of glucose control.

The most common adverse reactions to metformin are gastrointestinal but the most feared reaction, although rare, is lactic acidosis.^{5,9} A meta-analysis of 347 studies assessed the incidence of lactic acidosis in patients on metformin treatment for at least one month compared to placebo or non-metformin therapies.¹⁰ There were no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patients-years in the non-metformin group. The upper limit for the true incidence of lactic acidosis per 100,000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. In a subgroup of patients with mild to moderate CKD, there was no difference in the incidence of lactic acidosis. Furthermore, there is no correlation between levels of metformin and lactate in patients with lactic acidosis, and its prognosis is mainly related to the severity of the underlying condition and comorbidities.⁹ The risk of lactic acidosis is enhanced by conditions that cause hypoxia and which predispose patients to lactate production and accumulation such, as heart failure and pulmonary chronic disease, or diseases that reduce lactate clearance (e.g. liver dysfunction).

The evidence suggests that metformin can be safely used in patients with creatinine <1.5mg/dL. Since serum creatinine may overestimate renal function, calculation of the estimated GFR (eGFR) is preferred. The clearance of metformin decreases by about 75% when the eGFR is <60mL/min/1.73m² without additional changes when the eGFR declines to 30mL/min/1.73m².¹¹ At these levels of renal impairment, serum concentration of metformin is only about two-fold higher than in normal kidney function. Current United Kingdom (UK) guidelines on the treatment of T2DM allow metformin use until an eGFR of 30mL/min/1.73m² with dose reduction advised at

45mL/min/1.73m².^{9,12} In the USA, metformin is contraindicated for men with serum creatinine ≥1.5mg/dL and for women with serum creatinine ≥1.4mg/dL;⁵ eGFR calculated for these creatinine values ranges from 66mL/min/1.73m² in a 20-year-old man (54mL/min/1.73m² in a 20-year-old woman) to 43mL/min/1.73m² in an 80-year-old man (36mL/min/1.73m² in an 80-year-old woman).

A recent observational study of 51,675 T2DM patients with a mean follow-up of 3.9 years supports the NICE guideline recommendations.¹³ A composite endpoint including acidosis, shock, acute renal failure and serious infections was used to evaluate the occurrence of lactic acidosis. Metformin, compared with any other treatment, showed reduced risks of acidosis/serious infection and all-cause mortality in patients with eGFR 45-60mL/min/1.73m², and no increased risks of all-cause mortality, acidosis/serious infection or cardiovascular disease were found in patients with eGFR 30-45mL/min/1.73m². A prospective observa-

tional study evaluated acute kidney injury and lactic acidosis in patients treated with metformin.¹⁴ A total of 29 cases were identified over 4 years; however, moderate renal impairment was not associated with a higher risk of dialysis-dependent acute kidney injury in patients who develop lactic acidosis and it seems not to influence prognosis. In this study, an episode of acute gastroenteritis precipitated the event in 26 cases, showing that volume depletion and hypoperfusion appear to aggravate the severity of metformin-related metabolic acidosis when associated with an acute kidney injury.

Although the use of metformin in moderate CKD is still controversial, we think that its use should be avoided in patients with CKD stages 3-5 with other risk factors for lactic acidosis. In patients without risk factors, the available evidence suggests that metformin may be safely used without dose adjustment in CKD stage 3A and with half-dose reduction in stage 3B (Table 1). Patients should be encouraged to inter-

Table 1. Dosing adjustment for oral hypoglycemic drugs according to CKD stage

Class	Drug	Chronic kidney disease stage (dialysis not included)			
		3A 45-59 mL/min	3B 30-44 mL/min	4 15-29 mL/min	5 <15 mL/min
Biguanides	Metformin	No dose adjustment ¹	Half-dose ¹	Avoid	
Sulfonylureas	Glibenclamide	Avoid			
	Glipizide	No dose adjustment		No dose adjustment ²	
	Gliclazide				
	Glimepiride	Initiate at low dose (1mg)	Initiate at low dose (1mg) ²		
Meglitinide analogues	Nateglinide	No dose adjustment		Initiate at low dose (60mg)	Avoid
	Repaglinide	Initiate at low dose (0.5mg)			
Thiazolidinediones	Pioglitazone	No dose adjustment ³			
Alpha-glucosidase inhibitors	Acarbose	No dose adjustment		Avoid	
	Miglitol				
Dipeptidyl Peptidase-4 Inhibitors	Sitagliptin			50mg/day ⁴	25mg/day
	Vildagliptin	No dose adjustment ⁴		50mg/day ⁴	
	Saxagliptin	2.5mg/day ⁴			
	Alogliptin			12.5mg/day ⁴	6.25mg/day
	Linagliptin	No dose adjustment			

¹Avoid if patient has other risk factors for lactic acidosis; these levels are controversial.

²Glipizide is the preferred sulfonylurea; however, safer options which carry no risk of hypoglycemia should be considered.

³Although it is not contraindicated in patients with advanced CKD, the possibility of fluid retention and bone disease may limit its use.

⁴Dose adjustment required for GFR <50mL/min.

Adapted from National Kidney Foundation, 2012 KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis 60: 850-886.⁴

rupt their metformin treatment in the case of acute volume depletion such as gastroenteritis.

Sulfonylureas

Sulfonylureas bind to the SU receptor and close the K_{ATP} -dependent potassium channel in the pancreatic beta-cells, altering the resting potential of the cell.¹⁵ This leads to calcium influx and stimulation of insulin secretion. SUs are well absorbed and peak concentrations are reached within 1-4 hours. They are tightly bound to plasma albumin (90-99%) and have a small volume of distribution.¹⁶ Since SUs stimulate insulin secretion independent of blood glucose levels, they may cause hypoglycemia, especially the long-acting SUs.¹⁵ They may also reduce hepatic gluconeogenesis and glycogenolysis and increase glucose uptake in the liver and utilization in the skeletal muscles.

Glibenclamide is a long-acting (24h) SU metabolized in the liver, mainly to 2 metabolites (M1 and M2).¹⁷ In normally functioning humans, 30-60% of M1 and M2 are excreted in the urine and the rest by biliary secretion. M1 and M2 may have a hypoglycemic effect. In a study that evaluated the pharmacokinetics of a single dose (7mg) of glibenclamide in patients with CKD, very small amounts of M1 and M2 were excreted in urine in the renally impaired group and diabetic patients had slightly higher serum levels of metabolites than the normal function group.¹⁷ Neither glibenclamide nor its metabolites seemed to accumulate in patients with severe CKD after a single dose of glibenclamide, which may indicate that complementary non-renal elimination routes might operate in these subjects. However, during chronic therapy one or more metabolites may accumulate in patients with CKD, resulting in an increased risk of hypoglycemia.

Glipizide is rapidly absorbed, reaching peak concentrations after 1.5 hours.¹⁸ It undergoes hepatic metabolism in several inactive metabolites and elimination $t_{1/2}$ is 2-3 hours. However, the duration effect of a single dose of 7.5mg glipizide lasts around 12-14 hours. About 60% of glipizide is excreted as metabolites and less than 10% unchanged in urine. One study in two patients with a GFR of 30ml/min and 10 ml/min showed an increase of the $t_{1/2}$ of glipizide metabolites to 20h and more.¹⁹ Although several

metabolites accumulate in patients with CKD, they do not seem to cause an increased risk of hypoglycemia.²⁰ Of the second-generation SUs, glipizide is the preferred agent, since it does not increase the risk of hypoglycemia in patients with CKD.

Gliclazide is extensively metabolized into 7 inactive metabolites and mainly excreted in the urine.²¹ Renal insufficiency has little effect on the pharmacokinetic profile of gliclazide. Efficacy and safety of gliclazide modified release was evaluated in a double-blind trial over 2 years.²² Of the 507 T2DM patients who completed the study, 20% had mild to moderate CKD (CrCl 20-80mL/min) and no excess in frequency of hypoglycemia symptoms was observed in this subgroup. This was not related to a reduction in glycemic control, as final HbA1c was similar in the whole population. Gliclazide safety profile has been well established in clinical studies performed in patients with mild to moderate renal impairment.

Glimepiride is completely absorbed and undergoes extensive hepatic metabolism to the active M1 metabolite, with further dehydrogenation to the inactive M2 metabolite.²³ The elimination $t_{1/2}$ is about 5-8 hours. About 37-52% of a glimepiride dose is found in the urine as M1 or M2 within 48 hours, with the remainder appearing in feces. Although glimepiride clearance tends to increase in patients with CKD as creatinine clearance decreases, the terminal $t_{1/2}$ is unaffected. However, urinary clearance of its metabolites decreases with creatinine clearance.²⁰ Since prolonged hypoglycemia has been described in patients with CKD under glimepiride therapy, its use in this group of patients should be discouraged.

The recommendations for the use of SUs in patients with CKD are summarized in Table 1. Glibenclamide should be avoided in patients with moderate to severe CKD. Glipizide and gliclazide may be used in patients with CKD stages 3 to 5 without dose adjustment. Glimepiride may also be used in patients with CKD stages 3 and 4 with dose adjustment to a maximum of 1mg/day. However, caution must be taken in relation to the risk of hypoglycemia. Since T2DM patients with CKD often have other comorbidities and may be old and frail, safer alternatives are preferred.

Meglitinide analogues

Meglitinide analogues stimulate insulin release by inhibiting K_{ATP} -dependent channels of the β -cell membrane.²⁴ They are rapidly absorbed, stimulating insulin release within a few minutes, and are metabolized in the liver and mainly excreted in bile. Following preprandial administration, insulin is more readily available during and just after the meal, which leads to a reduction in postprandial hyperglycemia without the danger of hypoglycemia between meals.

Nateglinide reaches its peak plasma concentration in less than an hour.²⁵ It binds extensively (98%) to serum proteins and is predominantly metabolized by cytochrome P450 isoenzymes CYP2C9 (70%) and CYP3A4 (30%). Several metabolites have been identified in plasma and urine but only M1 has significant pharmacological activity. Most nateglinide pharmacological activity is attributed to the parent compound.²⁶ It is rapidly eliminated with a $t_{1/2}$ of 2.91 ± 1.84 hours. Between 20-30% of the dose is eliminated unchanged in the bile and urine. Approximately 2/3 is excreted in the feces and 1/3 in urine. Nateglinide is well tolerated and has a low risk of hypoglycemia.²⁷ In patients with CKD, a single dose of 90mg was safe and effective.²⁸ Compared to healthy subjects, patients with T2DM and moderate to severe CKD (CrCl 15-50mL/min) displayed similar clearance, AUC, and C_{max} .²⁹ Patients with T2DM on dialysis exhibited reduced overall drug exposure.³⁰ A pooled analysis of elderly patients with renal impairment ($n = 333$) did not reveal an increased incidence of confirmed hypoglycemia in this population.³¹ However, an increase in the levels of the active metabolite M1 occurs with decreased renal function, which may increase the risk of hypoglycemia. Evidence suggests that nateglinide may be safely used in patients with CKD stage 3, but in patients with a GFR <30 mL/min/1.73m² it should be initiated conservatively at 60mg with meals.

Repaglinide is rapidly absorbed with maximum concentrations attained within an hour.³² There is a high (68.8%) inter-individual variation in the AUC after multiple doses in patients with T2DM that may be explained by differences in activity of CYP450 enzymes that metabolize repaglinide. It is rapidly and completely metabolized to M1 and M2. No

metabolites with clinically relevant hypoglycemic effects have been identified.³² Repaglinide is primarily eliminated by the liver and its metabolites are biliary-fecal excreted. Within 96 hours, 90% of the drug is eliminated as metabolites via the feces and 8% in the urine. Repaglinide is generally well tolerated and hypoglycemic events are rare.³³ In patients with mild to moderate CKD, there are no clinically relevant effects in relation to the pharmacokinetics of repaglinide. In patients with T2DM and severe CKD, exposure to repaglinide appears to be elevated. Therefore, repaglinide may be safely used in CKD stage 3, but when GFR is <30 mL/min/1.73m² treatment should be started at a 0.5mg dose with each meal.³⁴

Thiazolidinediones

Thiazolidinediones activate the nuclear peroxisome proliferator activated receptor- γ (PPAR- γ), which is thought to be involved in the modulation of the expression of genes coding for proteins involved in glucose and lipid metabolism.³⁵ These proteins amplify the post-receptor actions of insulin in the liver and peripheral tissues, resulting in improved glycemic control with no increase in endogenous insulin secretion.³⁶ Since rosiglitazone was withdrawn from the European market in 2010 due to its potential risk of causing ischemic heart disease and is available in the US only with significant restrictions on prescription, we will focus our discussion on pioglitazone.

Pioglitazone is well absorbed after oral administration, with peak concentrations achieved approximately 1.5 hours later.³⁶ It is highly bound to plasma proteins and has a low tissue distribution and slow elimination ($t_{1/2}$ about 9 hours). It undergoes extensive hepatic metabolism and its major active metabolites, M-III and M-IV, have considerably longer terminal $t_{1/2}$ than the parent compound. It is excreted as inactive metabolites in the feces.

A study in 21 individuals with severe (CrCl <30 mL/min) or moderate (CrCl 30-60mL/min) CKD and 6 healthy volunteers receiving single and multiple doses of pioglitazone 45mg revealed no significant accumulation of the drug and its metabolites.³⁷ After single and repeated oral doses, mean AUC values were decreased in patients with severe CKD compared with healthy subjects for pioglitazone, M-III and M-IV metabolites. This may be explained by reduced protein

binding resulting in increased free pioglitazone. The tolerability and safety profile of pioglitazone was comparable between groups. In patients on hemodialysis, pioglitazone was effective and safe, with no increase in adverse effects.^{38,39} The most common adverse effects of pioglitazone are weight gain, fluid retention, a twofold increased risk of congestive heart failure, and an increase in fracture rates and bone loss.³⁶ The mechanism through which thiazolidinediones induce fluid retention is controversial. Most studies suggest that this effect results from the increase in tubular sodium and water reabsorption in the kidney, but the role of specific nephron segments and sodium carriers involved is less clear.⁴⁰ Some studies suggest that PPAR γ agonist stimulates Na(+) reabsorption in the collecting duct by activating the epithelial Na(+) channel (ENaC). Alternative mechanisms in the collecting duct include stimulation of non-ENaC sodium channel or inhibition of chloride secretion to the tubular lumen. In addition, thiazolidinediones may augment sodium reabsorption in the proximal tubule by stimulating the expression and activity of apical Na(+)/H(+) exchanger-3 and basolateral Na(+)-HCO₃(-) co-transporter, as well as that of Na(+)/K(+)-ATPase. These effects are mediated by PPAR γ -induced non-genomic transactivation of the epidermal growth factor receptor and downstream extracellular signal-regulated kinases (ERK).⁴⁰ Therefore, pioglitazone is not recommended in New York Heart Association (NYHA) Class III and IV heart failure.⁴¹ There is also some concern about a possible association with bladder cancer.⁴² Although no dose adjustment in patients with CKD stages 3 to 5 is recommended,⁴ its use in patients with CKD should be balanced with the possibility of worsening of fluid retention and fractures, the latter particularly in patients with underlying bone disease (such as renal osteodystrophy).

Alpha-glucosidase inhibitors

The α -glucosidase inhibitors bind reversibly to the oligosaccharide binding site of α -glucosidases, which are enzymes located in the brush-border membrane of the small intestine responsible for the digestion of complex polysaccharides and sucrose.⁴³ The inhibition of α -glucosidase delays the production of monosaccharides, reducing postprandial hyperglycemia and hyperinsulinemia. The main side effects, flatulence,

abdominal distension, and diarrhea, are more frequently reported in the first 3 months of treatment and seem to be dose-dependent.⁴⁴⁻⁴⁶

Acarbose is minimally absorbed in unchanged form and has extremely limited systemic availability.⁴³ It is extensively metabolized by gastrointestinal amylases and intestinal flora, yielding at least 13 metabolites, one of which has one third of acarbose activity. In subjects with normal renal function, 35% is recovered in urine and about 50% in feces. The elimination $t_{1/2}$ is about 2.8 hours, although a more slowly declining terminal phase exists with a $t_{1/2}$ of approximately 9 hours. Patients with CrCl <25mL/min/1.73m² attained peak plasma concentrations of acarbose which were about 5 times higher than volunteers with normal renal function. Their AUCs were 6 times greater than the volunteers'.⁴⁷ Acarbose is not recommended in patients with GFR <26mL/min/1.73m².⁴

Miglitol absorption is saturable at high doses and exhibits peak concentrations in 2-3 hours.⁴⁸ It is systemically absorbed rather than metabolized and it is eliminated by renal excretion as an unchanged drug. At doses higher than 25mg, the cumulative recovery of drug from urine is lower due to the incomplete bioavailability. The elimination $t_{1/2}$ of miglitol is approximately 2 hours. In patients with CKD, accumulation of miglitol is expected. Patients with CrCl <25 mL/min taking 25mg 3 times daily exhibited a greater than two-fold increase in miglitol plasma levels compared to subjects with CrCl >60mL/min. Little information is available on the safety of miglitol in patients with CrCl <25mL/min. Miglitol is not recommended in patients with GFR <25mL/min/1.73m².⁴

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors improve glycemic control by preventing the inactivation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.⁴⁹ The increase of incretin hormones stimulates insulin secretion and reduces postprandial glucagon in a glucose-dependent fashion. The first in class was sitagliptin approved in 2006, followed by vildagliptin in 2007, saxagliptin in 2009, alogliptin in 2010, and linagliptin in 2011.⁵⁰ These drugs are not more efficient in lowering blood glucose concentrations and reducing HbA_{1c} levels than the older molecules. Nevertheless, they offer

several clinical advantages.⁵ Among the most important are a negligible risk of hypoglycemia and a weight-neutral profile. These two side effects are clinically relevant since hypoglycemia is associated with increased mortality and, in patients losing weight, a 1% decrement in HbA1c was associated with an HR of 0.91 (0.83, 0.99) for the all-cause mortality endpoint.⁵¹ For participants not losing weight, each 1% decrease in HbA1c was associated with an HR of 1.00 (0.88, 1.15).⁵²

DPP-4 inhibitors are rapidly absorbed, with significant inhibition of plasma DPP-4 activity achieved within 5 minutes of administration.⁵⁰ All gliptins, except linagliptin, are poorly bound to plasma proteins.

Sitagliptin does not undergo appreciable metabolism; it produces 6 metabolites, 3 of these active, which do not seem to contribute to its pharmacodynamic profile.^{50,53} It is mainly excreted unchanged in the urine. A single-dose study was conducted to evaluate the pharmacokinetics of 50mg sitagliptin in patients with varying degrees of CKD compared to normal healthy controls.⁵⁴ Patients with mild CKD (CrCl 50-80 mL/min) did not have a clinically meaningful increase in the plasma concentration of the drug. In patients with moderate (CrCl 30-50mL/min) and severe CKD (CrCl <30mL/min), and in those on hemodialysis, a 2.3-, 3.8- and 4.5-fold increase in the plasma AUC of sitagliptin was observed and the terminal $t_{1/2}$ values were raised to 19.1, 22.5, and 28.4 hours, respectively. Sitagliptin was modestly removed by hemodialysis. In a 54-week randomized, double-blind trial which evaluated the safety and efficacy of sitagliptin in patients with T2DM and moderate to severe CKD and ESRD on dialysis, sitagliptin was generally well tolerated and effective.⁵⁵ The overall incidence of drug-related and serious adverse effects was similar between groups. In summary, sitagliptin dose adjustments are recommended for patients with T2DM and moderate to severe renal failure (50mg/day and 25mg/day, respectively), as for those on dialysis (25mg/day).^{54,56}

Vildagliptin is extensively metabolized into a major biologically inactive metabolite and 4 minor metabolites.⁵³ The main route of elimination is metabolism, with only approximately 25% of the drug excreted by the kidneys.⁵⁷ Vildagliptin has low po-

tential for drug to drug interactions because it does not inhibit or induce CYP enzymes.⁵⁶ Compared to subjects with normal renal function, in patients with mild, moderate, and severe CKD, and on hemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8-66%; AUC 32-134%). However, changes in exposure to vildagliptin did not correlate with severity of CKD. Exposure to the main metabolite increased with increasing severity of CKD (AUC 1.6- to 6.7-fold), but this effect did not have clinically relevant consequences as the metabolite is inactive. Elimination $t_{1/2}$ of vildagliptin was not affected by CKD.⁵⁸ In a prospective study of vildagliptin (50mg qd) in 515 T2DM patients with moderate (GFR \geq 30 to \leq 50mL/min/1.73m²) or severe CKD (GFR <30mL/min/1.73m²), treatment with vildagliptin added to ongoing diabetic therapy was well tolerated, with a safety profile comparable to placebo.⁵⁹ A prospective, open-label, parallel group, controlled study evaluated the efficacy and safety of vildagliptin in 51 Japanese diabetic patients undergoing hemodialysis.⁶⁰ After a 24-week period, no serious adverse effects such as hypoglycemia or liver impairment were observed in any patient. Vildagliptin was effective as a treatment for diabetic patients undergoing hemodialysis (decreased average HbA1c levels from 6.7% baseline to 6.1%, and average glycated albumin levels from 24.5% baseline to 20.5%, $p < 0.0001$). No dosage adjustment is required in patients with mild CKD (CrCl \geq 50mL/min).⁴ In patients with moderate or severe CKD or with ESRD, the recommended dose of vildagliptin is 50 mg once daily. Since there is limited experience in patients on hemodialysis, vildagliptin should be used with caution in these patients.

Saxagliptin is extensively metabolized, primarily by cytochrome P450 3A4/5.⁵⁶ The major metabolite (M2) has half the potency of saxagliptin. Saxagliptin and M2 are eliminated by hepatic and renal routes.⁶¹ In patients with mild CKD, the AUC of saxagliptin and M2 was 1.2- and 1.7- fold higher than in patients with normal renal function.⁶² This increase was not considered clinically relevant and no dosage adjustment is recommended. In patients with moderate or severe CKD, the AUC and M2 were up to 2.1- and 4.5- fold higher than in patients with normal renal function. A randomized 52-week trial conducted in 170 T2DM patients with CrCl <50mL/min or

ESRD, which evaluated the efficacy and safety of saxagliptin 2.5mg once daily versus placebo, showed a low frequency of mainly mild hypoglycemic events (28% versus 29%, respectively) and saxagliptin was well tolerated.⁶³ It has recently been demonstrated that saxagliptin is able to reduce the development and progression of microalbuminuria.⁶⁴ Patients with moderate to severe CKD should not receive more than 2.5mg/day; in patients with ESRD the drug can be taken after hemodialysis.^{4,62}

Alogliptin does not suffer appreciable metabolism and around 80% is eliminated unchanged in urine.⁵³ Metabolism of alogliptin is mediated by cytochrome P 450 to active (M-I) and inactive (M-II) metabolites. The results of a single dose (50mg) in patients with CKD showed an increase in alogliptin exposure in comparison with healthy volunteers: approximately 1.7-, 2.1-, 3.2-, and 3.8- fold, respectively, in patients with mild, moderate, severe CKD and in patients on dialysis.⁶⁵ It is advised that patients with moderate CKD should receive half of the recommended dose and patients with severe CKD or ESRD should receive a quarter of the dose.⁴

Linagliptin does not undergo appreciable metabolism.⁵³ Exposure to its major metabolite, which is inactive, was about 18% of the parent compound. A study investigating the pharmacokinetic profile of ¹⁴C-linagliptin demonstrated that after oral administration, 84.7% of the dose was excreted in feces, whereas renal excretion accounted for 5.4% of the dose.⁵⁰ Another study conducted in patients with and without T2DM with different degrees of CKD showed renal excretion <7% in all groups.⁶⁶ Under single-dose conditions, the degree of renal impairment did not affect plasma linagliptin concentration time profiles. Since renal excretion is a minor elimination pathway of linagliptin at therapeutic dose levels, a dose adjustment in patients with CKD is not required.⁴

Dopamine receptor agonist

Bromocriptine was first approved by the FDA in 1978 for the treatment of Parkinson's disease, hyperprolactinemia, and acromegaly.⁶⁷ Bromocriptine has now been reformulated into a quick-release formulation for the treatment of T2DM in adults and this formulation and indication were approved by the FDA in 2009. Although its mechanism of action

is unknown, bromocriptine mesylate improves postprandial glucose without increasing plasma insulin concentrations. Bromocriptine mesylate has a high bioavailability, between 65% and 95%, and reaches peak plasma concentrations in 45 to 60 minutes if taken on an empty stomach, later if taken after a meal.⁶⁸ It is 90-96% bound to plasma proteins and is extensively metabolized in the gastrointestinal tract and liver. The major route of bromocriptine excretion is in the bile with the remaining approximately 2-6% of an oral dose excreted via the urine. The elimination half-life is approximately 6 hours. Studies in patients with CKD are limited,⁶⁹ so it should not be used in patients with reduced GFR until more evidence is available.

Sodium-glucose co-transporter 2 inhibitors

The SGLTs are a family of membrane proteins which transport glucose across the brush-border membrane of the proximal renal tubule and across the intestinal epithelium.⁷⁰ SGLT1 and SGLT2 are the most studied co-transporters. Over 90% of filtered glucose is reabsorbed in the earlier segments of the proximal tubule via SGLT2; SGLT1, located in the distal segments, absorbs the remainder.⁷¹ A novel class of oral anti-diabetic drugs, the SGLT2 inhibitors, block the reabsorption of filtered glucose, leading to glycosuria with consequent glycemic control improvement.⁷² Dapagliflozin is the first drug in this class approved by the EMA. Improvements in glycemic parameters have been observed with dapagliflozin when administered as monotherapy, as in combination therapy, with a 10-mg dapagliflozin once-daily dose appearing to show the optimal benefit-risk profile.⁷³ In studies that evaluated the pharmacokinetics and pharmacodynamics of dapagliflozin, it demonstrated linear pharmacokinetics over the dose range of 2.5 to 500 mg and a dose-dependent increase in urinary glucose excretion over 24 hours.⁷⁴ Dapagliflozin was rapidly absorbed after oral administration and C_{max} were observed within 2 h. The mean t_{1/2} after the last dose ranged from 11.2 to 16.6h. A recent meta-analysis showed that in patients with moderate renal impairment, use of dapagliflozin was associated with increased incidence of renal-related adverse events.⁷⁵ A multicenter trial is ongoing to evaluate the glycemic efficacy, renal safety, pharmacokinetics, and pharmacodynamics of dapagliflozin in subjects with

T2DM and moderate CKD.⁷⁶ Although renal function does not seem to be affected,⁷⁷ its use in patients with moderate to severe CKD (CrCl <60ml/min or eGFR <60ml/min) is not recommended. Since the elimination depends on kidney function, dapagliflozin is less effective if GFR decreases.

G-protein coupled receptor 40 agonists

G-protein coupled receptors are a superfamily of membrane proteins activated by a variety of endogenous ligands such as hormones, neurotransmitters, peptides, proteins, steroids, fatty acids (FAs), and other lipids.⁷⁸ GPR40 is a member of this family, highly expressed in pancreatic β cells and in other insulin-secreting cell lines. FAs act as signaling molecules and have glucose-dependent insulinotropic effects mediated through activation of GPR40.⁷⁹ TAK-875 is a novel highly selective, orally available GPR40 agonist,⁸⁰ and in a study conducted in patients with T2DM it showed good tolerability with no dose-limiting side effects.⁸¹ TAK-875 showed reductions from baseline in fasting (2 to -93 mg/dl) and post-OGTT glucose (26 to -172 mg/dl), with an apparent dose-dependent increase in post-OGTT C-peptide over 14 days. Consistent with preclinical data, TAK-875 apparently acts as a glucose-dependent insulinotropic drug with low hypoglycemic risk. Currently, there are no data on the safety of TAK-875 in patients with CKD.

CONCLUSION

Treating T2DM patients with CKD is a great challenge. The increasing availability of different classes of oral glucose-lowering drugs requires physicians to be aware of their mechanism of action, pharmacokinetics, and safety. In addition, the recommendations on the use of the same agent according to the degree of renal impairment may differ between countries. While in the USA the use of metformin is contraindicated in men with serum Cr ≥ 1.5 mg/dL (and in women with serum Cr ≥ 1.4 mg/dL), its use is allowed in the UK until GFR of 45mL/min/1.73m², with dose adjustment advised for GFR between 30-45 mL/min/1.73m². Although the exact GFR cutoff for metformin use to avoid lactic acidosis is controversial, the benefit of its use in patients without other risk factors for lactic acidosis seems to outweigh its risks. Sulfonylureas are not all the same. Glibenclamide should be avoided in patients

with moderate to severe CKD. Glimepiride may be used in patients with CKD stages 3 and 4 with dose adjustment (1mg), but its use should be discouraged since there are less dangerous alternatives. Although glipizide and gliclazide may be used in patients with CKD stages 3 to 5 without dose adjustment, caution must be exercised due to the risk of hypoglycemia, and other classes with a safer profile should be favored. Nateglinide and repaglinide can be used in moderate to severe CKD, with dose adjustment advised for patients with GFR <30mL/min/1.73m² (nateglinide should be initiated at 60mg and repaglinide at 0.5mg dose, both with meals). Since pioglitazone is mainly hepatically eliminated, it may be used in patients with CKD in stages 3 to 5 without dose adjustment. However, caution should be taken with in regard to the development of fluid retention and worsening of bone disease. Acarbose and miglitol should not be used in patients with severe CKD. The DPP-4 inhibitors may all be used in moderate to severe CKD and in dialysis. Of these, linagliptin is the only one with insignificant renal elimination and it does not require dose adjustment. Fifty percent dose reduction is recommended for sitagliptin (50mg daily) and alogliptin (12.5mg) in patients with CrCl 30-50 mL/min and a 75% dose reduction (respectively 25mg and 6.25mg daily) for CrCl <30mL/min. Fifty percent dose reduction is also advised for vildagliptin (50mg daily) and saxagliptin (2.5mg daily) in patients with CrCl <50mL/min. Bromocriptine mesylate is a new drug approved for the treatment of T2DM but evidence in patients with CKD is scarce, so its use should be discouraged. Emerging classes of anti-diabetic drugs are in development, such as the SGLT inhibitors and the GPR40 agonists, but there are still no data on their potential use in patients with impaired renal function.

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