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REVIEW ARTICLE

Pharmacotherapy of Type 2 Diabetes Mellitus: An Update on Drug–Drug Interactions

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Abstract The incidence of type 2 diabetes mellitus is increasing rapidly, as are the associated co-morbidities. Consequently, it has become necessary for a diabetic patient to take multiple medications at the same time to delay progression of the disease. This can put patients at an increased risk of moderate to severe drug interactions, which may threaten patients' life or may deteriorate the quality of their life. Hence, managing drug–drug interactions is the cornerstone of anti-diabetic therapy. Most of the clinically important drug–drug interactions of anti-diabetic agents are related to their metabolic pathways, but drugs that compete for renal excretion or impair renal status can also play an important role. In this review, we have examined the clinical implications and underlying mechanisms of drugs that are likely to alter the pharmacologic response of or cause adverse events with antidiabetic drugs, and we have outlined safe and efficacious treatment modalities.

Key Points

Lactic acidosis is the main adverse event of concern associated with metformin therapy; however, the incidence of this adverse event is low. Any drug that deteriorates renal status of the patient or competes for renal excretion of metformin is likely to alter drug concentrations in the body, which may change pharmacologic response or cause adverse events.

Hypoglycemia is the main adverse event associated with sulfonylureas. Any drug that alters cytochrome P450 2C9 isozyme levels in the body is likely to modify the concentration of drug in the circulation, which may increase or decrease pharmacologic response and result in adverse events.

Edema and exacerbation/precipitation of heart failure are the main adverse events associated with thiazolidinedione use. Non-steroidal anti-inflammatory drugs, insulin, nitrates, and sulfonylureas are likely to have an adverse effect.

Generally, drug interaction potential of incretin mimetics and sodium glucose co-transporter 2 inhibitors is low, which makes these drugs a suitable choice in managing type 2 diabetes mellitus and associated complications. However, the long-term safety of these agents is not known.

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1 Introduction

Diabetes mellitus is a world-wide epidemic that is increasing at an alarming rate, mostly owing to a decrease

in physical activity and an increase in the incidence of obesity. It is estimated that by 2030, diabetic patients will increase to approximately 550 million world-wide [1]. Type 2 diabetes will account for almost 90 % of the cases. As type 2 diabetes progresses, the patient becomes unresponsive to lifestyle changes. A single drug is no longer sufficient and combination therapies are subsequently required to achieve the desired glycemic goals. This combination therapy is not limited to anti-diabetic drugs as the patient now becomes prone to many micro- and macrovascular complications [2]. Thus, a diabetic patient commonly receives therapeutic agents such as antihypertensive, antiplatelet, and lipid-lowering drugs in addition to antibiotics and antifungal agents, especially in the older population because of reduced immunity [3]. As the pharmacokinetic and pharmacodynamic characteristics of each drug are different, one drug can increase or decrease another drug's pharmacologic response or alter the adverse-effect profile. This process is commonly referred to as drug–drug interaction (DDI). In a DDI, a pair of drugs is involved known as a precipitant drug and an object drug. It is the precipitant drug that alters the activity of the object drug in the process.

Based upon the underlying mechanisms involved, DDIs are characterized as either pharmacokinetic or pharmacodynamic [4]. In pharmacokinetic interactions, the precipitant drug alters the absorption, distribution, metabolism, or excretion (ADME) of the object drug causing an alteration in its response, while in pharmacodynamic interactions, an alteration in response is noticed without any change in the ADME profile of the object drug [4]. A synergistic blood glucose-lowering effect of combination therapy of metformin and a sulfonylurea agent is a common example of a pharmacodynamic interaction. In clinical practice, we are mostly concerned with pharmacokinetic interactions. However, the importance of pharmacodynamic interactions should not be underestimated as these interactions can severely deteriorate the patients' status in certain circumstances, e.g., hypoglycemic risk of sulfonylureas increases in combination therapies with other antidiabetic agents as compared with sulfonylurea monotherapy. Most of the drug interactions associated with antidiabetic drugs are related to either inhibition or induction of metabolic pathways, but drugs affecting the renal status of the patient also play an important role. It should be kept in mind that drug interactions involving the induction of enzymes are usually delayed-onset interactions as synthesis of the new enzyme may take some time, but drug interactions involving the inhibition of an enzyme are usually rapid-onset interactions.

In this review, we focus on the clinical implications, mechanisms, and management of clinically important DDIs of antidiabetic agents that are commonly used in the pharmacotherapy of type 2 diabetes.

2 Biguanides

Among biguanides, metformin is the only agent currently used in clinical practice. It is the first-line therapeutic agent in the treatment of type 2 diabetes in addition to lifestyle interventions [5]. Metformin works mainly by inhibiting gluconeogenesis in the liver. It increases tissue sensitivity by promoting insulin binding to its receptor sites and inducing phosphorylation of glucose transporters in skeletal muscles [6]. Thus, it reduces blood glucose levels without affecting insulin secretion. Therefore, hypoglycemic risk is rarely associated with metformin use. Metformin is partially absorbed from the small intestine and about 80–100 % of the drug is excreted unchanged mainly in urine through active tubular secretion [7]. This indicates metformin is not metabolized significantly. Moreover, protein binding of the drug in plasma is also low. Elimination of the drug is largely dependent on renal function of the patient as it is the substrate for many cation transporters in the kidney [8]. The main cation transporters involved in the transport of metformin are organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) 1 and MATE2K [8]. Pharmacokinetic characteristics of metformin have been summarized in Table 1.

Adverse effects of the drug are mostly gastro-intestinal system related, e.g., nausea, vomiting, diarrhea, and flatulence; however, a potentially life-threatening adverse event, lactic acidosis, may occur with metformin use especially in patients with certain risk factors, which may result in a mortality rate of nearly 50 % [8, 9]. However, the incidence of lactic acidosis with metformin therapy is low, which is thought to be about 3.3 cases per 100,000 person-years [10]. Metformin inhibits gluconeogenesis, therefore it increases the levels of its precursor lactate in the blood. Normally, plasma lactate concentrations remain in the physiologic limits owing to its clearance by the kidneys and other mechanisms in the body, but in the presence of risk factors such as renal impairment the plasma concentrations of metformin as well as lactate become high [11]. The risk of lactic acidosis increases if plasma metformin concentrations increase above 20 mg/L but in patients with risk factors it may also occur at lower concentrations [12]. Another adverse event of concern especially with long-term metformin therapy is inhibition of vitamin B_{12} absorption in a small segment of patients, which may or may not manifest in the form of anemia and peripheral neuropathy [13, 14]. Careful monitoring is required as permanent neuronal damage may occur if not diagnosed in time. Vitamin B_{12} supplementation may be required in such a condition; alternatively, calcium supplements are reported to improve vitamin B_{12} absorption [15].

Table 1 Pharmacokinetic characteristics of antidiabetic drugs

Drug	Bioavailability (%)	Protein binding (%)	Metabolism	Excretion
Metformin [8]	55	Negligible	Not significant	Urine: 80–100 % excreted unchanged
Gliclazide [25]	97	95	Major: CYP2C9	Mainly urine
			Minor: CYP2C19	
Glipizide [25]	80	95	CYP2C9	Urine: 63–90 %
				Feces: 11 %
Glibenclamide [25]	90	99	CYP2C9 and CYP3A4[a]	Urine: 50 %
				Bile: 50 %
Glimepiride [25]	100	>99	CYP2C9	Urine: 60 %
				Feces: 35 %
Pioglitazone [56]	>80	>99	Major: CYP2C8	Mainly feces
			Minor: CYP3A4	Urine: 15–30 %
Rosiglitazone [57]	≈100	>99.8	Major: CYP2C8	Urine: ≈64 %
			Minor: CYPC9	Feces: ≈23 %
Sitagliptin [70]	87	38	Not significant	Urine: 87 %
			Minor: CYP3A4 and CYP2C8	Feces: 13 %
Vildagliptin [70]	85	9	Hydrolysis, oxidation, no CYP enzyme involved	Urine: 85 %
				Feces; 4.5 %
Saxagliptin [70]	67[b]	Very low	CYP3A4/5	Urine: 75 %
				Feces: 22 %
Linagliptin [70]	30	>80	Not significant	Urine: 5 %
			Minor: CYP3A4	Enterohepatic system: 80 %
Alogliptin [70]	100	20	Not significant	Urine: 76 %
			Minor: CYP3A4 and CYP2D6	Feces: 13 %
Exenatide [88]	65–76		Proteolytic degradation	Mainly urine
Liraglutide [90]	55	>98	Proteolytic degradation	Metabolized endogenously. Urine 6 % and feces 5 % in the form of metabolites
Dapagliflozin [102]	78	91	Glucuronidation	Mainly urine and to a lesser extent feces
Canagliflozin [103]	65	99	Glucuronidation	Mainly feces and to a lesser extent urine

[a] Contribution of CYP3A4 in glibenclamide metabolism is not clearly known, [b] Predicted

CYP cytochrome P450

2.1 Drugs Affecting Plasma Concentrations of Metformin

Any drug that deteriorates the renal status of the patient or competes for renal excretion is likely to alter metformin concentrations in the body, which may change the pharmacologic response or alter the profile of adverse events. Therefore, patients should be monitored carefully for any adverse event while co-administering ACE inhibitors, loop diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, or cyclosporine with metformin. In addition, drug interactions have been reported with some other drugs within this category. Cimetidine, a cationic drug is reported to compete for renal excretion of metformin through active tubular secretion that may involve OCT2- or MATE1-dependent pathways [8]. In healthy subjects, cimetidine significantly increased the peak serum concentration (C_{max}) of the drug by 81 % and the area under the plasma-concentration time curve (AUC) by 50 %. The renal clearance of the drug was decreased by 27 % [16]. In patients receiving such combination therapy, it is prudent to observe the patient for the development of any adverse event especially lactic acidosis. The blood glucose levels should be monitored and metformin dose reduced, if necessary [17]. However, such an interaction is of limited importance as there is only one case report of lactic acidosis where cimetidine may have played a role in development of this disease condition [18]. Other cationic drugs such as procainamide, digoxin, amiloride, quinine, quinidine, ranitidine, trimethoprim, and vancomycin also share the same mechanism for renal excretion; therefore, the same precautionary measures should also be taken if co-administered with metformin [19]. However, the clinical significance of these expected drug interactions is not exactly known (Table 2).

Table 2 Summary of drug interactions associated with metformin therapy

Precipitant drug	Clinical implication	Mechanism	Management	Clinical significance
Drugs affecting plasma concentrations of metformin				
Cimetidine[a] [16]	↑ In metformin levels; ↑ in response and adverse events	MATE1, MATE2K inhibition	Monitor blood glucose levels and observe patient for any adverse event; reduce dose if required	Low
Cephalexin [20]	↑ In metformin levels; ↑ in response and adverse events	MATE1, MATE2K inhibition	Monitor blood glucose levels and observe patient for any adverse event or change antibiotic	Uncertain
Pyrimethamine [21]	↑ In metformin levels; ↑ in response and adverse events	MATE1, MATE2K inhibition	Monitor blood glucose levels and observe patient for any adverse event; reduce dose if required	Low
Anticholinergic drugs [22]	↑ In metformin levels; ↑ in response and adverse events	↑ Absorption due to ↓ GI motility	Monitor blood glucose levels and observe patient for any adverse event; reduce dose if required	Low
Drugs associated with risk of lactic acidosis				
Iodinated contrast media [23]	↑ In metformin levels; ↑ in risk for MALA	CMN	Contraindicated. Stop metformin 48 h before contrast media administration and initiate 48 h after contrast media administration	High

CMN contrast media-induced nephrotoxicity, *MALA* metformin-associated lactic acidosis, *MATE* multidrug and toxin extrusion transporter; ↑ increase; ↓ decrease

[a] Cationic drugs such as procainamide, digoxin, amiloride, quinine, quinidine, ranitidine, trimethoprim, and vancomycin also share the same mechanism for renal excretion; therefore, patients should be observed carefully for changes in blood glucose concentrations and for the development of any adverse event

Cephalexin has also been reported to significantly increase the C_{max} and AUC of metformin by 34 and 24 %, respectively, as well as decreasing its renal clearance by 14 % in healthy volunteers [20]. This interaction could be a matter of concern if such a combination is used long term (Table 2). Similarly, pyrimethamine, a MATE inhibitor, also increased the AUC of metformin by 39 % while it reduced renal clearance by 35 % in healthy subjects [21]. If such a combination is administered, it is recommended to monitor blood glucose levels and adverse events and subsequently make necessary adjustments in the dose when required (Table 2). Clinically, this interaction is also of limited importance as no case of lactic acidosis has been reported with such a combination.

In another pharmacokinetic study, the anticholinergic drug propantheline caused a non-significant increase in the AUC of metformin while the percentage of drug excreted unchanged in urine was increased significantly [22]. The most likely mechanism involved in this interaction is a decrease in GI motility, which increased the transit time of the drug in the intestine thus increasing its absorption [22]. In such cases, patients need careful monitoring while initiating and stopping anticholinergic therapy. However, the clinical relevance of this interaction is minor (Table 2).

2.2 Drugs Associated with the Risk of Lactic Acidosis

Of all the interactions discussed above, the most important DDI of metformin is with iodinated contrast media, which is considered to have a strong association with lactic acidosis because of its potential to cause contrast media-induced nephrotoxicity [23]. Patients with risk factors such as renal impairment, hepatic impairment, and tissue hypoxic conditions are thought to be at a higher risk for this life-threatening condition. Therefore, co-administration of these agents is contraindicated and metformin therapy should be stopped at least 48 h before contrast media administration and restarted 48 h after administration of iodinated contrast media (Table 2) [17, 23].

Although co-administration of these agents is not recommended, the risk of lactic acidosis in patients without risk factors is extremely low. In a systematic review of literature, it was noticed that out of 18 cases of lactic acidosis, 17 cases occurred in patients with renal insufficiency or with other contraindications to metformin therapy [24]. There was only one case of lactic acidosis due to this combination in a patient with normal renal function [24]. However, this suggests that the risk of lactic acidosis in this combination regimen cannot be ruled out in patients without risk factors.

3 Sulfonylureas

Sulfonylureas are second-line therapeutic agents in the pharmacotherapy of type 2 diabetes, which are used if the patient is intolerant to or does not respond to metformin monotherapy [5]. These agents act by inhibiting adenosine triphosphate-dependent potassium channels in the β cells. This results in an increased influx of extracellular calcium

into the β cells by opening L-type calcium channels causing insulin release by acting upon insulin secretory vesicles. This action of sulfonylureas is independent of plasma glucose levels, therefore, hypoglycemia is the main adverse event associated with these drugs [25]. First-generation sulfonylureas are rarely used in clinical practice these days. Therefore, second-generation sulfonylureas such as gliclazide, glipizide, glibenclamide, and glimepiride are of interest in this category. These drugs have very high bioavailability and are metabolized in the liver mainly by cytochrome P450 (CYP) 2C9 and to a lesser extent by CYP2C19 and CYP3A4 [26]. These agents are highly protein bound and excreted largely through urine followed by feces. Thus, any drug that affects the ADME profile of sulfonylureas has the potential to alter the pharmacologic response and the risk of adverse events of these drugs [26, 27]. Table 1 presents the summary of pharmacokinetic characteristics of second-generation sulfonylureas.

3.1 Drugs Likely to Increase the Risk of Hypoglycemia

Although sulfonylureas have long been used successfully with other antidiabetic agents, this therapeutic class has a strong potential for drug interactions with other pharmacologic agents that are commonly used by a diabetic patient. Therapeutic agents such as azole antifungals (fluconazole, ketoconazole, miconazole) and the fibrate agents, e.g., gemfibrozil, are strong inhibitors of CYP2C9 isozyme in the liver [28–31]. These agents have a potential to increase the plasma levels of the CYP2C9 substrates such as sulfonylureas by inhibiting their metabolism. This causes an increased risk of hypoglycemia, which necessitates close monitoring of blood glucose levels and careful observation of the patient for symptoms of hypoglycemia. This is an established drug interaction of clinical importance but the incidence of adverse events is uncertain. However, concurrent use of these agents needs not be avoided. Instead precautionary measures need to be taken. Patient needs to be warned of the hypoglycemic risk and dose adjustment of the sulfonylureas may be required based upon patients' responses (Table 3) [17, 28–31].

Salicylates such as aspirin increase the pharmacologic response and hypoglycemic risk of sulfonylureas by displacing them from their protein-binding sites [32]. The interaction between salicylates and sulfonylureas has gained more importance these days owing to a wide use of aspirin in diabetic patients. Although severe hypoglycemia is unlikely in such cases, monitoring of blood glucose levels is required to avoid hypoglycemic risk. Reduction in dose of the sulfonylurea may be necessary especially if a patient is using high doses of salicylates (Table 3).

There are two case reports of hypoglycemia in older patients with type 2 diabetes receiving a sulfonylurea drug and clarithromycin. Both patients had impaired renal function and had a mildly low albumin level [33]. Increase in the concentration of the free drug owing to low albumin levels and/or renal impairment was likely to play a role in this interaction. Clinical importance of this interaction is uncertain but caution is recommended while co-administering a macrolide with a sulfonylurea. Blood glucose monitoring may be helpful and the dosage of sulfonylurea drug may be adjusted accordingly (Table 3) [17].

ACE inhibitors are reported to increase hypoglycemic risk by increasing tissue sensitivity owing to their vasodilatory effect [34]. Although this interaction is not well recognized as the risk of severe hypoglycemia is low, such cases have been reported in patients receiving this combination. It is therefore prudent to monitor blood glucose levels especially when starting ACE inhibitor therapy as well as counseling the patient about symptoms of hypoglycemia. Dose reduction of the sulfonylurea may be required based upon patients' responses to therapy (Table 3) [17, 34]. Ethanol has an established drug interaction with sulfonylureas because of its ability to decrease gluconeogenesis process in the liver, which prolongs the hypoglycemic effect of sulfonylureas [35]. Such patients need to be advised to avoid alcohol use while receiving sulfonylurea therapy. If they cannot abstain, alcohol intake should be limited and the patient should be counseled to avoid alcohol intake on an empty stomach [17]. Patients should also be advised about the warning signs of hypoglycemic onset. Physicians and pharmacists should keep in mind that some of the symptoms of hypoglycemia may be masked owing to alcohol use and the patients need to be advised accordingly (Table 3) [17, 35]. Case reports of severe and life-threatening hypoglycemia have been reported with quinolone antibiotics in patients receiving a sulfonylurea [36, 37]. Nonetheless, the clinical relevance of this drug interaction is uncertain and likely to be minor. It is however preferable to avoid co-administration of both these drugs. If co-administered, the patient should be observed very carefully for symptoms of hypoglycemia [17]. The mechanism behind this interaction is not completely understood, although an increase in insulin secretion has been observed in such cases (Table 3).

Histamine H_2-receptor antagonists especially cimetidine have also been reported to increase the plasma drug concentration of sulfonylureas; therefore, blood glucose monitoring may be needed in patients receiving such combination therapies [38]. The most likely mechanism is inhibition of hepatic metabolism. However, clinical importance of this interaction is low as there are studies that show cimetidine and ranitidine have no clinically important effect on the pharmacokinetics of sulfonylureas (Table 3) [17].

Magnesium salts increase hypoglycemic risk by promoting absorption of sulfonylureas possibly by increasing

Table 3 Summary of drug interactions associated with sulfonylurea therapy

Precipitant drug	Clinical implication	Mechanism	Management	Clinical significance
Drugs likely to increase risk of hypoglycemia				
Ketoconazole [28]	↑ In hypoglycemic risk	CYP2C9 inhibition	Monitor blood glucose levels Dose reduction of SU drug may be required	Moderate
Fluconazole [29]	↑ In hypoglycemic risk	CYP2C9 inhibition	Monitor blood glucose levels Dose reduction of SU drug may be required	Moderate
Miconazole [30]	↑ In hypoglycemic risk	CYP2C9 inhibition	Monitor blood glucose levels Dose reduction of SU drug may be required	Moderate
Fibrates [31]	↑ In hypoglycemic risk	CYP2C9 inhibition	Monitor blood glucose levels Dose reduction of SU drug may be required	Moderate
Salicylates [32]	↑ In hypoglycemic risk	Displacement of SU drug from protein-binding sites	Monitor blood glucose levels Observe patients for symptoms of hypoglycemia	Low. Caution is recommended with high doses
ACE inhibitors [34]	↑ In hypoglycemic risk	↑ In tissue sensitivity due to vasodilation	Observe patients for symptoms of hypoglycemia	Low
Ethanol [35]	Prolonged hypoglycemia	Inhibition of gluconeogenesis	Counsel patients to limit intake and avoid drinking on an empty stomach Advise about symptoms of hypoglycemia	High
Quinolones [36, 37]	Severe hypoglycemia may occur	Unknown	Observe patients for symptoms of hypoglycemia	Low, but caution required
H2 Antagonists[a] [38]	↑ In hypoglycemic risk	CYP2C9 inhibition	Observe patients for symptoms of hypoglycemia	Low
Magnesium Salts [39]	↑ In hypoglycemic risk	↑ In gastric pH	Administer SU drug 0.5–1 h before antacid	Uncertain
Phenylbutazone and Azapropazone [41, 43]	↑ In hypoglycemic risk	CYP2C9 inhibition, displacement from protein-binding sites and inhibition of renal excretion	Monitor blood glucose levels for phenylbutazone Dose reduction of SU drug may be required Co-administration of azapropazone and SU drugs is not recommended	Moderate
Sulfonamides [45]	↑ In hypoglycemic risk	CYP2C9 inhibition and displacement from protein-binding sites	Monitor blood glucose levels Advise patient about the symptoms of hypoglycemia	Uncertain
Chloramphenicol [46]	↑ In hypoglycemic risk	CYP2C9 inhibition	Monitor blood glucose levels Advise patient about the symptoms of hypoglycemia	Moderate
Heparin [47]	↑ In hypoglycemic risk	Displacement from protein-binding sites	Monitor patient for symptoms of hypoglycemia	Low
DPP-4 Inhibitors [48]	↑ In hypoglycemic risk	Possible synergistic effect	Reduce dose of SU agent	Moderate
GLP-1 Analogues [49]	↑ In hypoglycemic risk	Possible synergistic effect	Reduce dose of SU agent	Moderate
Drugs likely to decrease pharmacologic response				
Rifampicin [50]	↓ In efficacy Blood glucose levels may ↑	CYP2C9 induction	Monitor blood glucose levels Dose increase of SU drug may be required	Moderate

Table 3 continued

Precipitant drug	Clinical implication	Mechanism	Management	Clinical significance
Cholestyramine [51]	↓ In efficacy Blood glucose levels may ↑	Impaired absorption of SU agent	Administer SU agent 1–2 h prior to cholestyramine	Unknown. Limited data available
Colesevelam [52]	↓ In efficacy Blood glucose levels may ↑	Impaired absorption of SU agent	Administer SU agent 3–4 h prior to colesevelam	Unknown. Limited data available
Non-selective B-blockers [53]	↓ In efficacy Blood glucose levels may ↑	Possibly, blockade of beta-2 receptors in pancreas	Observe patient for ↑ in blood glucose levels Advise about symptoms of hypoglycemia not affected by beta blockade Use of a cardio-selective B-blocker preferable	Moderate
Bosentan [54]	Hepatotoxicity ↓ In efficacy likely	↑ In liver amino-transferases	Contraindicated Use alternative	High

[a] Cimetidine is the most likely precipitant drug being the inhibitor of CYP2C9

CYP cytochrome P450, *SU* sulfonylurea, ↑ increase, ↓ decrease

gastric pH, thereby enhancing solubility of the drug. Although the clinical significance of this interaction is uncertain, such interactions have been reported in healthy subjects. If an interaction is suspected, administration of the sulfonylurea drug 0.5–1 h before antacid intake is the recommended measure to avoid any adverse event (Table 3) [17, 39]. Glucose-lowering effects of sulfonylureas have also been increased by co-administration of phenylbutazone and azapropazone and some cases of hypoglycemia have been reported [40–42]. The mechanism is not fully understood but evidence suggests that inhibition of the metabolism, displacement of the sulfonylurea drug from its binding site, and inhibition of renal excretion may play a role [41, 42]. Drug interaction with phenylbutazone is well documented and is of clinical importance. Therefore, it is recommended to monitor blood glucose levels and make necessary adjustments in the dose accordingly (Table 3) [40–42]. Although studies with azapropazone and sulfonylureas are limited, azapropazone should not be used with sulfonylureas according to manufacturers' recommendations [43].

Similarly, sulfonamides are reported to enhance blood-lowering effects of sulfonylureas by possibly inhibiting their metabolism and also by displacing them from their protein-binding site [44, 45]. The clinical importance of this interaction is not certain as not all the sulfonamides have equal potential to inhibit CYP2C9 metabolism in the liver. However, it is recommended to monitor blood glucose levels and educate the patient of the risks and symptoms associated with hypoglycemia (Table 3) [17, 44, 45]. Similarly, chloramphenicol is reported to increase hypoglycemic risk by inhibiting metabolism of sulfonylureas in the liver [46]. Although studies were conducted with the first-generation sulfonylurea, it is recommended to monitor blood glucose levels in patients taking second-generation sulfonylureas because the mechanism involved in the interaction is likely to also enhance plasma concentrations of the second-generation sulfonylureas [17]. The incidence of adverse events is uncertain but this is an established drug interaction of clinical importance (Table 3). An isolated report of hypoglycemia was reported in a hospitalized diabetic patient when heparin was added to glipizide [47]. Displacement of the drug from its protein-binding site was suspected. Although clinical importance of this interaction is small, this possibility should be kept in mind in patients receiving heparin with a sulfonylurea (Table 3) [47]. Dipeptidyl peptidase-4 (DPP-4) inhibitors and Glucagon-like peptide-1 (GLP-1) analogs are reported to increase hypoglycemic risk if used in combination with sulfonylureas, most probably owing to a synergistic effect [48, 49]. Therefore, it is recommended to monitor blood glucose levels and reduce the dose of sulfonylurea accordingly (Table 3).

3.2 Drugs Likely to Decrease Pharmacologic Response

In addition to the drug interaction discussed above, there are many drug interactions associated with sulfonylurea therapy that are likely to decrease pharmacologic response. CYP2C9 inducers such as rifampicin induce the CYP enzymes in the liver, which decreases the plasma concentrations of sulfonylureas causing a reduction in drug efficacy [50]. Documentation of this interaction is established despite the fact data are limited on the topic. In such cases, close monitoring of blood glucose levels is required to observe hyperglycemia and a higher dose of sulfonylurea drug may be required to meet the target glycemic levels [17]. The same precautionary measures should also be

taken while administering other CYP2C9 inducers with a sulfonylurea, as alterations in the pharmacokinetic profile of sulfonylureas may occur (Table 3).

The bile acid-binding resin, cholestyramine, is reported to decrease the pharmacologic response by impairing the absorption of sulfonylureas from the GI tract [51]. In the case of co-administration of cholestyramine, sulfonylureas should be administered at least 1–2 h prior to cholestyramine administration and blood glucose levels of the patient need to be monitored to avoid hyperglycemia [17]. Another bile acid-binding agent, colesevelam, has also been reported to decrease absorption of sulfonylureas. Therefore, the sulfonylurea should be administered at least 4 h prior to colesevelam as well as monitoring blood glucose levels [17, 52]. Because the clinical relevance of such interactions is unknown and data are very limited, it is recommended to take precautionary measures as mentioned above (Table 3).

A decrease in the efficacy of sulfonylureas has been noticed by unknown mechanisms when used in combination with a non-selective beta blocker [53]. However, blockade of beta-2 receptors in β cells is suspected in this case, which may impair insulin release [53]. Although the risk of hypoglycemia is rare in such combination therapy, a non-selective beta blocker may blunt the hypoglycemic symptoms that may increase the risk of a hypoglycemic event. In such cases, a selective beta blocker is preferable and patients receiving non-selective beta blockers need to be monitored for symptoms of hypoglycemia that are not affected by the beta blockade, e.g., diaphoresis. Nevertheless, blood glucose monitoring should be performed to ensure effective glucose control (Table 3) [17].

Bosentan is reported to increase the risk of hepatic toxicity if used in combination with glibenclamide, as well as decreasing its C_{max} and AUC and being an inducer of CYP2C9 and CYP3A4. Therefore, co-administration of both these drugs is not recommended [54]. Although studies are not available with other agents in the class to predict the risk of hepatotoxicity, CYP2C8/3A4 induction indicates the possibility of a reduced pharmacologic response in CYP2C9/3A4 substrates. Therefore, it is preferable to use an alternate agent (Table 3).

4 Thiazolidinediones

Pioglitazone and rosiglitazone are the two drugs of clinical importance in this category. Rosiglitazone has been withdrawn from the market in various countries including the European Union because of an increased risk of cardiovascular adverse events; however, it is still available in the USA with restrictions. The drug cannot be sold without a prescription and can be acquired by mail through indicated pharmacies.

Thiazolidinediones act by binding to peroxisome proliferator-activated receptor-γ, which increases insulin sensitivity in adipose, hepatic, and skeletal muscles [6]. Therefore, the incidence of hypoglycemia is low in this class of drugs. The most likely adverse event is peripheral and rarely results in pulmonary edema and/or precipitation/exacerbation of heart failure. The mechanism associated with this adverse event is the sodium-retention property of these agents [55]. Metabolism is hepatic with the major involvement of the CYP2C8 isozyme, while CYP3A4 and CYP2C9 isozymes have minor involvement [56, 57]. Bioavailability of pioglitazone is more than 80 % while that of rosiglitazone is above 99 % [56, 57]. Protein binding of the drug in plasma is more than 99 %. Pioglitazone is primarily eliminated through feces, followed by urine while rosiglitazone is primarily eliminated by urine and the rest by feces [56, 57]. This profile of thiazolidinediones indicates that any drug that alters CYP2C8 metabolism, displacement from protein binding sites, or renal elimination especially in the case of pioglitazone, can interfere with pharmacologic response and adverse events. However, DDIs reported with thiazolidinediones are mostly metabolic pathway related. A summary of pharmacokinetic characteristics of thiazolidinediones has been presented in Table 1.

4.1 Drugs Affecting Plasma Concentrations of Thiazolidinediones

Although azole antifungals such as ketoconazole and fluconazole are strong inhibitors of CYP2C9, CYP2C19, and CYP3A4 isozymes, they are weak inhibitors of CYP2C8. Nonetheless, ketoconazole has been reported to increase the AUC and the half-life of rosiglitazone significantly in healthy subjects [58]. Therefore, patients receiving such combination therapy need to be monitored for the development of any adverse event such as edema as well as monitoring blood glucose levels (Table 4) [17, 58]. Gemfibrozil, which is a strong inhibitor of both CYP2C8 and CYP2C9, has been reported to significantly increase both the half-life and AUC of pioglitazone in healthy volunteers [59]. Interestingly in the same study, itraconazole, which is a strong inhibitor of CYP3A4, had no clinically important effect on the AUC and half-life of pioglitazone [59]. Gemfibrozil produced similar results in a study with rosiglitazone [60]. The clinical importance of all these interactions is uncertain; however, caution is recommended especially with rosiglitazone. A better measure would be to avoid co-administration of these agents altogether. If this cannot be done, thiazolidinedione therapy should be initiated at a lower dose (Table 4) [17, 59, 60]. In addition, blood glucose levels should be monitored and patients should be observed for development of any

Table 4 Summary of drug interactions associated with thiazolidinedione therapy

Precipitant drug	Clinical implication	Mechanism	Management	Clinical significance
Drug affecting plasma concentrations of thiazolidinedione agents				
Ketoconazole [58]	↑ In response and risk for adverse events	CYP2C8 inhibition	Monitor blood glucose levels and observe patient for any adverse event	Uncertain
Gemfibrozil [60]	↑ In response and risk for adverse events	CYP2C8 inhibition	Avoid co-administration If cannot, administer TZD at a lower dose	Uncertain
Rifampicin [61]	↓ In response	CYP2C8 induction	Monitor blood glucose levels	Uncertain
Fluvoxamine [63]	↑ In response and risk for adverse events	CYP2C8 inhibition	Monitor blood glucose levels and observe patient for any adverse event	Low
Trimethoprim [64]	↑ In response and risk for adverse events	CYP2C8 inhibition	Monitor blood glucose levels and observe patient for any adverse event	Uncertain
Drugs associated with risk of cardiovascular events				
Insulin[a] [66]	↑ Incidence of edema, hypoglycemia, and possibly myocardial infarction	Unknown Possible synergistic effect	Observe closely for an adverse event if pioglitazone is used Rosiglitazone is not recommended for co-administration with insulin	High
NSAIDS [67]	↑ Risk for edema and heart failure	Possible synergistic effect	Observe closely for symptoms of heart failure	High
Sulfonylureas[b] [67]	↑ Incidence of edema, heart failure, and hypoglycemia	Unknown	Avoid TZDs with SU drugs Use only as second-line therapy	High
Nitrates[a] [67]	↑ Risk for myocardial ischemia	Unknown	Avoid TZDs in patients with myocardial ischemia Co-administration of rosiglitazone is not recommended	High

CYP cytochrome P450, *SU* sulfonylurea, *TZDs* hiazolidinedione, ↑ increase, ↓ decrease

[a] Incidence of myocardial ischemia has been reported with rosiglitazone only, [b] Incidence of edema and heart failure is reported with rosiglitazone only

adverse event [17]. Another drug interaction is reported with rifampicin, which is an inducer of CYP isozymes in liver including CYP2C8. Rifampicin has been reported to significantly decrease the AUC of pioglitazone by 54 % and half-life by 53 %; however, at the same time, AUC of its active metabolite M-IV was increased by 131 % [61]. Similar results were also noticed with rosiglitazone [62]. The combined effect of these pharmacokinetic changes on the patient status is not exactly known, therefore it is not possible to predict any change in response. However, blood glucose monitoring is recommended in patients receiving this combination (Table 4) [17]. The selective serotonin reuptake inhibitor, fluvoxamine, which is a weak inhibitor of CYP2C8, has been reported to significantly increase the AUC of rosiglitazone in the range of 12–25 % and prolong the half-life by 2 h while the AUC of its metabolite *N*-desmethylrosiglitazone remained unaltered [63]. CYP2C8 genotypes had no significant influence on the pharmacokinetics of rosiglitazone in this study [63]. Although the increase in AUC was moderate, patients receiving such a combination need monitoring for blood glucose levels and for the development of adverse events [17, 63]. Clinical importance of this interaction is likely to be low (Table 4). Trimethoprim, which is an inhibitor of CYP2C8, significantly increased the AUC and half-life of pioglitazone by 42 and 32 %, respectively [64]. Similar results have also been observed in a trimethoprim rosiglitazone study [65]. The clinical relevance of this interaction is not exactly known but close monitoring of both blood glucose levels and the development of any adverse event such as edema and heart failure is recommended (Table 4) [17, 64].

4.2 Drugs Associated with the Risk of Cardiovascular Events

Thiazolidinediones have many drug interactions of clinical importance that have been linked to edema and cardiovascular adverse events. Insulin is such example that seems to have a pharmacodynamic interaction with thiazolidinediones. In a randomized controlled trial of rosiglitazone in a group of patients with inadequate glycemic control with insulin therapy, a higher incidence of hypoglycemia and edema was noticed in comparison with placebo [66]. The incidence of edema was 13.1 % and 16.2 % for rosiglitazone 4- and 8-mg dosage strengths, respectively, vs. 4.7 % in the placebo group. Likewise, the incidence of

hypoglycemia was 53 % and 67 % for two dosage strengths of rosiglitazone while only 38 % of patients experienced hypoglycemia in a placebo-treated group [66]. Although these results are not conclusive, an increased incidence of myocardial infarction has also been observed with rosiglitazone and insulin combination studies [67]. Therefore, according to manufacturers' recommendations, co-administration of rosiglitazone and insulin is not recommended (Table 4). Whereas NSAIDs have no pharmacokinetic interaction with thiazolidinediones but both drugs can cause fluid retention that can precipitate heart failure. Therefore, it is recommended to be cautious when this combination is used and patients should be observed closely for symptoms of heart failure (Table 4) [17]. Combination therapy with sulfonylureas increases hypoglycemic risk. In addition, rosiglitazone in combination with a sulfonylurea has reported to increase the incidence of edema and heart failure [67]. Therefore, this combination is recommended only when a patient is intolerant to or unresponsive to metformin and sulfonylurea combination therapy (Table 4). Combination therapy with nitrates may increase the risk of myocardial ischemia mostly in patients with coronary heart diseases [67]. In a meta-analysis study, the odds ratio for myocardial ischemia was 2.9 in the group of patients receiving both rosiglitazone and nitrates in comparison to controls, while in the rosiglitazone-only group odds ratio for this event was 1.3 when compared with controls [67]. The risk of this adverse event is not similar for pioglitazone. The recommended precautionary measure is to avoid this combination in patients with myocardial ischemia (Table 4).

5 Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors are a new class of oral antidiabetic drugs approved for use in type 2 diabetes that act by inhibiting degradation of intestinal enzyme GLP-1 [68, 69]. GLP-1 is secreted in response to meals and stimulates insulin secretion by activating its G-protein-coupled receptor in β cells. It has been observed that in type 2 diabetes, the secretion of this enzyme is decreased [68]. GLP-1 is a substrate of DPP-4 and inhibition of DPP-4 by this new class of drugs inhibits its degradation and promotes insulin secretion in a glucose-dependent manner. Therefore, the risk of hypoglycemia is very low with their use in diabetic patients [69]. The drugs approved in the class in different parts of the world are sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

Metabolism of DPP-4 inhibitors in the liver is low except for saxagliptin and it is secreted unchanged mostly in urine [70]. The role of CYP enzymes in their metabolism is negligible. However, saxagliptin is a substrate of CYP3A4/5 and produces a metabolite that retains nearly half of the parent drugs' activity [70]. Vildagliptin is metabolized mainly by glucuronidation, hydrolysis, and oxidation with no involvement of CYP enzymes [70]. Excretion of these drugs is predominantly though the renal pathway except for linagliptin, which has a very low renal excretion [70]. Bioavailability is variable for each drug from 30 % for linagliptin to 87 % for sitagliptin. They are not highly bound to plasma proteins, except for linagliptin [70]. These drugs are not reported to induce or inhibit the CYP enzyme system [70]. Table 1 presents the summary of pharmacokinetic characteristics of DPP-4 inhibitors.

The above profile of DPP-4 inhibitors indicates that as a class of drugs their potential for a DDI is very low. However, saxagliptin possesses the propensity for a change in the pharmacokinetic profile if used in combination with a CYP3A4/5 inducer or inhibitor. Pharmacokinetic studies have been conducted for almost all the drugs in the class with antidiabetic drugs such as metformin, sulfonylurea, and pioglitazone but no clinically relevant interaction has been reported [71–76]. However, the incidence of hypoglycemia is increased if used in combination with a sulfonylurea drug that is not unexpected [48]. Therefore, a lower dose of sulfonylurea may be required if used in combination with a DPP-4 inhibitor [48]. Similarly, the studies with other class of drugs such as simvastatin, digoxin, and warfarin have also been proven safe with no clinically significant changes in pharmacokinetics of either drug [77–82]. However, for patients receiving digoxin in combination with sitagliptin, monitoring of patients is recommended according to prescribing information as a slight increase in AUC of digoxin was observed. This increase was not considered clinically relevant by investigators [79]. Vildagliptin had no clinically significant interaction when co-administered with amlodipine, valsartan, and ramipril in healthy subjects [83]. However, a meta-analysis study has reported that the odds ratio for angioedema is high for vildalgliptin/ACE inhibitor combination therapy in comparison to controls, although the absolute risk was small [84]. No information is available in this regard for other drugs in the class.

As mentioned earlier, saxagliptin is the drug in the class that has a potential for drug interactions, being a substrate of CYP3A4/5 [70]. Saxagliptin has been studied in combination therapies with metformin, glibenclamide, and pioglitazone and no clinically relevant change in the pharmacokinetics of either drug has been noticed [74]. When saxagliptin was co-administered with simvastatin, a substrate of CYP3A4, C_{max} and AUC of saxagliptin was increased by 21 and 12 %, respectively, while corresponding values for its metabolite increased by 8 and 2 %, respectively, which was not considered clinically relevant [85]. In the same study, diltiazem, a moderate inhibitor of

CYP3A4, the same parameters of saxagliptin were increased by 63 and 109 % while C_{max} and AUC of its active metabolite was decreased by 43 and 34 %, respectively [85]. When a strong inhibitor of CYP3A4 ketoconazole was co-administered with saxagliptin in the same study, C_{max} and AUC of saxagliptin was increased by 62 and 145 %, respectively, while corresponding values of its metabolite were decreased by 95 and 88 %, respectively [85]. Based upon the above data, the author is of the opinion to use the lower dose of the drug when saxagliptin is used in combination with a strong CYP3A4 inhibitor. However, for diltiazem, dose reduction was not considered necessary [85]. Therefore, it is recommended to use 2.5-mg once-daily dose when a strong CYP3A4 inhibitor such as ketoconazole, itraconazole, clarithromycin, indinavir, nelfinavir, or ritonavir is used. Saxagliptin has also been studied with a strong CYP3A4 inducer rifampicin [86]. Although rifampicin decreased the C_{max} and AUC of saxagliptin, the overall DPP-4 inhibition was the same in the two study groups. Therefore, dose adjustment was not considered necessary [86]. Saxagliptin has not been studied with other CYP3A4/5 inducers such as phenytoin, carbamazepine, and phenobarbital; therefore, it is difficult to predict the response. Such patients should be observed carefully for any change in plasma concentrations of the drug or blood glucose levels.

6 Glucagon-like Peptide-1 Analogs

Exenetide and liraglutide are two agents currently available in the GLP-1 group for the treatment of type 2 diabetes. Both drugs are available in the form of subcutaneous injections. As discussed above, GLP-1 is secreted from the GI tract in response to meals and stimulates insulin secretion [68]. GLP-1 analogs are homologous to endogenous GLP-1 and retain many of its gluco-regulatory actions [87]. The incidence of hypoglycemia is low owing to its glucose-dependent action. Most of the adverse events are GI system related. Exenetide is reported to retain 53 % of homology while liraglutide retains nearly 97 % of homology to endogenous GLP-1 [87, 88]. However, GLP-1 analogs have long half-lives in comparison to endogenous GLP-1, which has a plasma half-life of 1–2 min only [88]. Exenatide has a minimal systemic metabolism and undergoes proteolytic degradation following glomerular filtration [89]. Liraglutide undergoes generalized proteolytic degradation and no single organ is responsible for its elimination from the body [90]. Exenatide has a bioavailabilty of 65–76 % while liraglutide has a bioavailability of nearly 55 %. Exenatide is predominantly excreted via the renal pathway while liraglutide is metabolized endogenously and only 6 % of the drug is excreted via the urine in the form of metabolites. In addition, only 5 % of the drug is excreted via the feces in the form of metabolites [90]. Pharmacokinetic characteristics of GLP-1 analogs have been summarized in Table 1.

The pharmacokinetic properties of these drugs indicate a low potential for DDIs. GLP-1 analogs have been successfully studied as add-on therapies to metformin, sulfonylureas, and thiazolidinediones [49, 91–93]. No clinically relevant impacts on the pharmacokinetics of either drug have been noticed. However, in sulfonylurea combination therapy, the incidence of hypoglycemia was high. Therefore, a lower dose of a sulfonylurea is recommended if used as add-on therapy to a GLP-1 analog [49]. Exenatide has been studied with lovastatin, warfarin, and digoxin in healthy subjects [94–96]. Clinically significant changes have not been noticed, therefore dose adjustment is not recommended in such combinations. In a study with paracetamol, exenatide decreased the rate of absorption of paracetamol but the extent of absorption remains unaffected [97]. Similar results were also observed when liraglutide was co-administered with paracetamol [98]. The underlying mechanism is a delay in gastric emptying time by GLP-1 analogs. Liraglutide has also been successfully studied in combination therapies with atorvastatin, digoxin, griseofulvin, lisinopril, ethinylestradiol, and levonorgestrel [99]. Minor changes were observed in the pharmacokinetics of these drugs but this did not warrant any dosage adjustment.

7 Sodium Glucose Co-transporter 2 Inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors are the latest antidiabetic agents approved for oral use in type 2 diabetes. Dapagliflozin is the first agent in the class that has been granted marketing authorization in Europe followed by USA while canagliflozin, the second agent in the class, was first authorized for marketing in USA followed by Europe. SGLT2 inhibitors are a novel class of antidiabetic agents that act by inhibiting absorption of glucose from the proximal convoluted tubule of nephron and enhancing urinary glucose excretion [100]. This unique mechanism of action reduces plasma glucose levels in an insulin-independent manner. Therefore, hypoglycemia is very rare and most of the adverse events associated with this class are genitourinary infections and related to osmotic diuresis/volume depletion [101–103]. However, as per the available data, these adverse events are not of a serious nature. Bioavailability of dapagliflozin is 78 % while that of canagliflozin is 65 % [102, 103]. Protein binding of the drug in plasma is very high; however, these drugs are not expected to be affected by protein-binding displacement interactions. SGLT2 inhibitors are metabolized in the liver

by glucuronidation process mediated by uridine 5'-diphospho-glucuronosyltransferase (UGT) without any involvement of the CYP enzyme system [102, 103]. Excretion of dapagliflozin is primarily in urine while the majority of the canagliflozin dose is excreted in feces [102, 103]. Table 1 presents the summary of pharmacokinetic characteristics of SGLT2 inhibitors.

The pharmacokinetic profile of SGLT2 inhibitors also suggests a low propensity of drug interactions. Studies have been conducted with other antidiabetic drugs such as metformin, sulfonylureas, thiazolidinediones, and DPP-4 inhibitors without any significant effect on the pharmacokinetic profile of either drug [104, 105]. Dapagliflozin has been studied with valsartan, digoxin, warfarin, and simvastatin but no clinically significant pharmacokinetic interaction has been observed [106]. Similarly, the UGT inducer rifampicin and UGT inhibitor mefenamic acid had no clinically relevant impact on the pharmacokinetics of dapagliflozin [107]. However, when canagliflozin was administered with the UGT inducer rifampicin, the AUC of canagliflozin was reduced by $\approx$50 %, which was considered clinically relevant [105]. Therefore, if the patient is tolerant, it is recommended to administer a 300-mg dose of the drug with UGT inducers such as rifampicin, ritinovir, and phenytoin [105]. Although canagliflozin had no clinically relevant interaction with warfarin in healthy subjects, exposure of digoxin was increased by $\approx$36 % [108]. Therefore, close monitoring of patients is recommended if such a combination is administered.

8 Drug Interactions Commonly Associated with all Antidiabetic Agents

In addition to the drug interactions mentioned above for specific categories of antidiabetic agents, there are some interactions that are commonly associated with all the antidiabetic drugs. These interactions have been categorized as follows:

8.1 Drugs Likely to Increase Pharmacologic Response

Anabolic steroids such as nandrolone, testosterone, methandienone, and stanozolol are reported to increase insulin sensitivity and enhance blood glucose-lowering effects of antidiabetic drugs [109, 110]. However, there is also evidence that anabolic steroids decrease insulin sensitivity and impair glucose tolerance. Therefore, the clinical picture of this interaction is not clear and not all the androgens have been studied for this effect. Blood glucose monitoring is recommended in such patients to make dosage changes of antidiabetic drugs, if required (Table 5) [17, 109].

Orlistat improves glucose tolerance probably by decreasing body weight, which may necessitate a reduction in the dose of antidiabetic drugs especially in overweight and obese diabetic patients [111]. Therefore, it is recommended to monitor blood glucose levels and make necessary adjustments in the dose of antidiabetic drugs (Table 5). Although ethanol has an established pharmacodynamic interaction with insulin and sulfonylureas, caution is also recommended with other antidiabetic drugs. As discussed earlier, ethanol inhibits gluconeogenesis and decreases blood glucose levels in the post-absorptive phase, therefore it increases hypoglycemic risk and masks many symptoms of hypoglycemia [112]. Ethanol has also been associated with alterations of counter-regulatory responses of hypoglycemia such as glucagon release [112]. Therefore, it is recommended to limit alcohol intake and it should be ingested with food and patients should be warned about the hypoglycemic risk (Table 5).

8.2 Drugs Likely to Decrease Pharmacologic Response

Antipsychotic drugs such as chlorpromazine, haloperidol, clozapine, olanzapine, and risperidone are reported to be associated with an increased risk for glucose intolerance [113, 114]. In a case-controlled study of older patients with diabetes hospitalized for inadequate glucose control, it was observed that co-administration of drugs such as quetiapine, olanzapine, and risperidone were associated with an increased risk of hyperglycemia especially during the first month of therapy [115]. The mechanism behind this interaction is decreased insulin secretion, increased adrenaline release, and most probably weight gain associated with antipsychotic therapy, which is likely to increase tissue resistance [113–115]. This is an established well-recognized drug interaction of moderate clinical severity. In view of the above discussion, it is prudent to monitor blood glucose levels of diabetic patients especially during the starting and stopping of antipsychotic therapy and to make dosage adjustments of antidiabetic drugs as necessary (Table 5).

Thiazide diuretics are thought to decrease the insulin sensitivity and/or decrease insulin secretion due to potassium loss, which may require an increase in the dose of the antidiabetic drug [116]. This is an established but moderate-severity delayed-onset drug interaction that may take days to months to exhibit its effects completely (Table 5).

Corticosteroids with glucocorticoid activity have been reported to impair glucose tolerance [117]. This is an established interaction with systemic corticosteroid use but a case report has also been reported with inhaled use of fluticasone in a 67-year-old diabetic patient taking metformin and glibenclamide [118]. There seems to be a direct antagonism between antidiabetic drugs and corticosteroid

Table 5 Summary of drug interactions associated with all antidiabetic drugs

Precipitant drug	Clinical implication	Mechanism	Management	Clinical significance
Drugs likely to increase pharmacologic response				
Anabolic steroids [109]	↑ In hypoglycemic risk	↑ Insulin sensitivity	Monitor blood glucose levels Adjust dose of antidiabetic drug if required	Uncertain
Orlistat [111]	↑ In hypoglycemic risk	↑ Insulin sensitivity	Monitor blood glucose levels Adjust dose of antidiabetic agent if required	High
Ethanol [112]	Prolonged hypoglycemia	Inhibition of gluconeogenesis	Counsel patients to limit intake and avoid drinking on an empty stomach Advise about symptoms of hypoglycemia	High
Drugs likely to decrease pharmacologic response				
Antipsychotics [113, 114]	Impaired glucose tolerance	↓ Insulin release, ↑ adrenaline, weight gain	Monitor blood glucose levels Adjust dose of antidiabetic agent if required	High
Thiazide diuretics [116]	↓ In efficacy Blood glucose levels may ↑	↓ In insulin sensitivity, insulin secretion, or K^+ loss	Observe patient for ↑ in blood glucose levels ↑ in SU drug may be required	High
Glucocorticoids [117]	Impaired glucose tolerance	Direct antagonism	Monitor blood glucose levels Adjust dose of antidiabetic agent if required	High
Hormonal contraceptives [120]	Impaired glucose tolerance	↑ GH, cortisol, altered tissue glucose use	Monitor blood glucose levels Adjust dose of antidiabetic agent if required	High
Nicotinic acid [124]	Impaired glucose tolerance	↑ In tissue resistance	Monitor blood glucose levels Adjust dose of antidiabetic agent if required	High
Calcineurin inhibitors [126, 127]	Post-transplant diabetes mellitus	↑ In tissue resistance, ↓ insulin release	Monitor blood glucose levels Use of insulin is preferred	High

GH growth hormone, *SU* sulfonylurea, ↑ increase, ↓ decrease

use. Nonetheless, very few studies are available on the topic most probably because of its established effect on glucose intolerance. In a case-controlled study in a group of patients taking glucocorticoids, it was noticed that the relative risk of hyperglycemia requiring therapeutic intervention was 2.23 compared with controls (Table 5) [119].

Hormonal contraceptives are reported to decrease pharmacologic response to antidiabetic drugs, although glycemic levels are not seriously altered [120]. Pharmacokinetic studies of hormonal contraceptives such as ethinylestradiol, levonorgestrel, and norethisterone have reported no clinically relevant changes on the pharmacokinetic profile of antidiabetic drugs such as pioglitazone, rosiglitazone, exenatide, and sitagliptin [121, 122]. Nonetheless, it is a well-documented moderate-severity drug interaction. The most likely mechanism involved in the interaction is an increase in growth hormone level, cortisol secretion, and altered glucose use by the body tissues (Table 5) [123].

Nicotinic acid is thought to impair glucose tolerance by aggravating tissue resistance to insulin. It is a well-known drug interaction of moderate severity. In a small, randomized controlled crossover study with type 2 diabetic patients, nicotinic acid is reported to increase glycosylated hemoglobin by 21 % and mean plasma glucose levels by 16 % [124]. Similar observations have also been noticed in other studies (Table 5) [125].

For all the drug interactions mentioned above, it is recommended to monitor blood glucose levels and make necessary adjustments in the dose of antidiabetic drugs if required. This monitoring may also be required in non-diabetic patients receiving glucocorticoid therapy [17].

Calcineurin inhibitors are reported to cause post-transplant diabetes mellitus (PTDM) in patients receiving solid organ transplant [126, 127]. A decrease in insulin release and an increase in insulin resistance are considered to play a role in this disease condition. The incidence of PTDM is 4.9 and 15.9 % in liver transplant patients, 4.7 and 11.5 %

in kidney transplant patients, and 15 and 17.5 % in lung transplant patients receiving cyclosporin A- and tacrolimus-based therapeutic regimens, respectively [126, 127]. Therefore, patients receiving such combination therapies need to be monitored closely for a decrease in pharmacologic response and an increased dosage if required (Table 5). The antidiabetic drugs may also need to be changed depending upon the potential of pharmacokinetic or pharmacodynamic interaction with calcineurin inhibitors. The safety of thiazolidinediones, incretin mimetics, and SGLT2 inhibitors needs to be determined in combination with this class of drugs, whereas sulfonylureas have the potential of drug interactions with these agents. Therefore, insulin remains a preferable choice in patients with such a clinical picture.

9 Conclusion

The above discussion reveals that most of the drug interactions associated with antidiabetic drugs are related to either inhibition or induction of metabolic enzymes. Pharmacokinetic studies on the topic do not encompass all the inducers/inhibitors of that particular metabolic pathway. Therefore, if a drug interaction is suspected with a specific agent in the class, it is expected that similar pharmacokinetic changes shall also occur with other agents affecting the same metabolic pathway in a similar manner. In addition, drug interactions involving renal elimination pathways and pharmacodynamic mechanisms also play an important role in eliciting a DDI of clinical importance. It stands at the core of diabetes therapy to identify interacting drugs and take preventative measures to avoid any undesirable effect.

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