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Drug Interactions of Clinical Importance with Antihyperglycaemic Agents

An Update

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Abstract

Because management of type 2 diabetes mellitus usually involves combined pharmacological therapy to obtain adequate glucose control and treatment of concurrent pathologies (especially dyslipidaemia and arterial hypertension), drug-drug interactions must be carefully considered with antihyperglycaemic drugs. Additive glucose-lowering effects have been extensively reported when combining sulphonylureas (or the new insulin secretagogues, meglitinide derivatives, i.e. nateglinide and repaglinide) with metformin, sulphonylureas (or meglitinide derivatives) with thiazolidinediones (also called glitazones) and the biguanide compound metformin with thiazolidinediones. Interest in combining

α-glucosidase inhibitors with either sulphonylureas (or meglitinide derivatives), metformin or thiazolidinediones has also been demonstrated. These combinations result in lower glycosylated haemoglobin (HbA_{1c}), fasting glucose and postprandial glucose levels than with either monotherapy. Even if modest pharmacokinetic interferences have been reported with some combinations, they do not appear to have important clinical consequences. No significant adverse effects, except a higher risk of hypoglycaemic episodes that may be attributed to better glycaemic control, occur with any combination. Challenging the classical dual therapy with sulphonylurea plus metformin, there is a recent trend to use alternative dual combinations (sulphonylurea plus thiazolidinedione or metformin plus thiazolidinedione). In addition, triple therapy with the addition of a thiazolidinedione to the metformin-sulphonylurea combination has been recently evaluated and allows glucose targets to be reached before insulin therapy is considered. This triple therapy appears to be safe, with no deleterious drug-drug interactions being reported so far.

Potential interferences may also occur between glucose-lowering agents and other drugs, and such drug-drug interactions may have important clinical implications. Relevant pharmacological agents are those that are widely coadministered in diabetic patients (e.g. lipid-lowering agents, antihypertensive agents); those that have a narrow efficacy/toxicity ratio (e.g. digoxin, warfarin); or those that are known to induce (rifampicin [rifampin]) or inhibit (fluconazole) the cytochrome P450 (CYP) system. Metformin is currently a key compound in the pharmacological management of type 2 diabetes, used either alone or in combination with other antihyperglycaemics. There are no clinically relevant metabolic interactions with metformin, because this compound is not metabolised and does not inhibit the metabolism of other drugs. In contrast, sulphonylureas, meglitinide derivatives and thiazolidinediones are extensively metabolised in the liver via the CYP system and thus, may be subject to drug-drug metabolic interactions. Many HMG-CoA reductase inhibitors (statins) are also metabolised via the CYP system. Even if modest pharmacokinetic interactions may occur, it is not clear whether drug-drug interactions between oral antihyperglycaemic agents and statins may have clinical consequences regarding both efficacy and safety. In contrast, a marked pharmacokinetic interference has been reported between gemfibrozil and repaglinide and, to a lesser extent, between gemfibrozil and rosiglitazone. This leads to a drastic increase in plasma concentrations of each antihyperglycaemic agent when they are coadministered with the fibric acid derivative, and an increased risk of adverse effects.

Some antihypertensive agents may favour hypoglycaemic episodes when coprescribed with sulphonylureas or meglitinide derivatives, especially ACE inhibitors, but this effect seems to result from a pharmacodynamic drug-drug interaction rather than from a pharmacokinetic drug-drug interaction. No, or only modest, interferences have been described with glucose-lowering agents and other pharmacological compounds such as digoxin or warfarin. The effects of inducers or inhibitors of CYP isoenzymes on the metabolism and pharmacokinetics of the glucose-lowering agents of each pharmacological class has been tested. Significantly increased (with CYP inhibitors) or decreased (with CYP inducers) plasma levels of sulphonylureas, meglitinide derivatives and thiazolidinediones have been reported in healthy volunteers, and these pharmacokinetic changes may lead to enhanced or reduced glucose-lowering action, and thus hypoglycaemia or worsening of metabolic control, respectively. In addition, some case reports have

evidenced potential drug-drug interactions with various antihyperglycaemic agents that are usually associated with a higher risk of hypoglycaemia.

Hyperglycaemia in type 2 diabetes mellitus results from a dynamic interaction between defects in insulin secretion and insulin action.[1] Type 2 diabetes is characterised by a progressive deterioration of the metabolic status over time, that essentially results from a progressive decline of insulin secretion, which becomes insufficient to compensate for insulin resistance.[2] Therefore, the management of the disease usually requires a stepwise adjustment of oral pharmacological therapies in combination with lifestyle modifications, and ultimately may lead to insulin requirement.[3-5] Such a strategy includes a progressive increase in the daily doses of each agent used and/or appropriate combinations of various glucose-lowering agents with complementary modes of action.[3,6,7] It may be speculated that initial combination therapy may be useful in order to target the various metabolic defects present in this complex disease (defective insulin secretion, increased hepatic glucose production, decreased muscular glucose utilisation) and thus avoid, or at least delay, the progressive and apparently inevitable deterioration of metabolic control seen over time in the majority of patients with type 2 diabetes.

Besides hyperglycaemia, other abnormalities are frequently present in patients with type 2 diabetes and are most probably related to visceral adiposity,[8] especially the atherogenic dyslipidaemia, arterial hypertension and prothrombotic state. All of these abnormalities are at least partially related to insulin resistance and to well documented cardiovascular risk factors.[9] The management of the so-called metabolic syndrome is crucial, especially in patients with type 2 diabetes.[10,11] Consequently, therapeutic guidelines for the management of type 2 diabetes should not only focus on the correction of hyperglycaemia, but rather should encourage the clinician to consider patients globally and to treat all risk factors present in each individual.[12] The use of a polypill to target several cardiovascular risk factors simultaneously has been suggested and may be appealing in patients with type 2 diabetes, although such a strategy remains hypothetical and controversial.[13]

Clearly there has been an impressive trend in the complexity of diabetes care, including polypharmacy, in the last decade.[14] Because management of diabetes usually involves combined pharmacological therapy and treatment of concurrent pathologies, drug-drug interactions with antihyperglycaemic agents must be carefully considered. Since a review on drug interactions of clinical importance with antihyperglycaemic agents published almost 10 years ago,[15] several new oral antidiabetic agents have been launched, especially new insulin secretagogues (compounds of the meglitinide family, i.e. nateglinide and repaglinide) and new insulin sensitisers (thiazolidinediones, which are also called glitazones, i.e. pioglitazone and rosiglitazone).[16] Consequently, the number of potential drug combinations for treating patients with type 2 diabetes has markedly increased during recent years.[3,6] In addition, new compounds are now available among well known antidiabetic classes, including the sulphonylureas (glimepiride) and α-glucosidase inhibitors (miglitol, voglibose). Furthermore, new fixed-dose combined formulations (metformin/glibenclamide [glyburide], metformin/glipizide, metformin/rosiglitazone) have been commercialised recently, at least in some countries. Finally, further reports of drug-drug interactions with classical compounds such as second-generation sulphonylureas (glibenclamide, glipizide, gliclazide) and acarbose, the first available α-glucosidase inhibitor, have been published during the last decade, as well as drug-drug interactions between new oral agents (glimepiride, repaglinide, nateglinide, pioglitazone, rosiglitazone, miglitol, voglibose) and other pharmacological compounds.

This review provides an update on clinically important drug-drug interactions with antihyperglycaemic agents. It is based upon published data only, after an exhaustive survey of the international literature. To identify relevant studies, we searched MEDLINE, EMBASE, Science citation index (Web of Science and ISI Proceedings) from January 1995 to December 2004 (period following our last review on the same topic[15]). The following keywords were

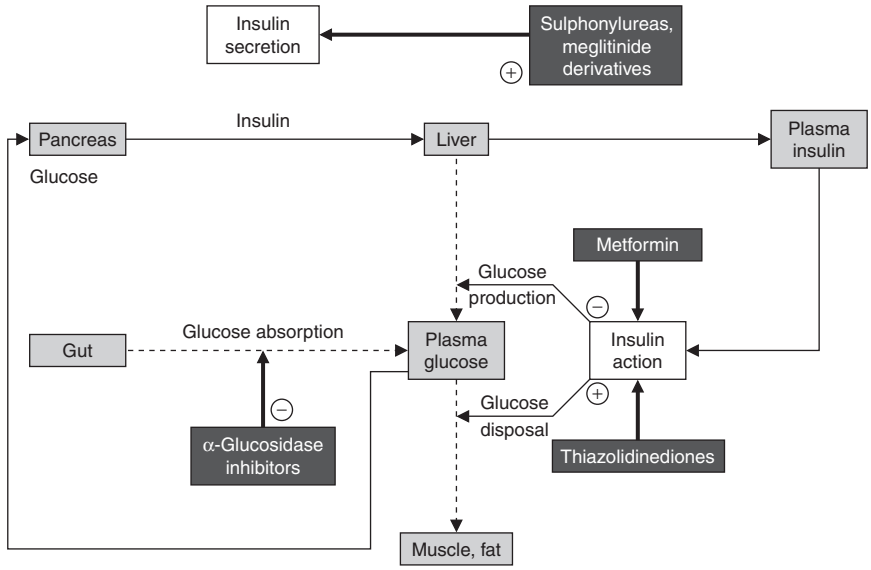

Fig. 1. Combination therapy with oral antihyperglycaemic agents acting on various metabolic/hormonal abnormalities in order to improve blood glucose control in patients with type 2 diabetes mellitus.

used: 'oral antidiabetic agents', 'drug interactions' and 'diabetes'. In addition, each name of a antihyperglycaemic compound was introduced, together with the item 'drug interaction', i.e. glibenclamide or glyburide, gliclazide, glimepiride, gliquidone, repaglinide, nateglinide, metformin, troglitazone, rosiglitazone, pioglitazone, acarbose, miglitol, voglibose. We also systematically checked the reference lists of identified studies using this initial search method in order to identify any additional trials that assessed the potential drug interactions with antidiabetic agents.

Information from any unpublished work or unpublished case reports was not taken into account. In the first section, pharmacokinetic and pharmacodynamic interactions between different antidiabetic agents will be considered, as such combinations are increasingly used for the treatment of patients with type 2 diabetes. In the second section, potential interferences that may occur between glucose-lowering agents and other drugs will be described. These other drugs considered are widely coadministered in diabetic patients (e.g. lipid-lowering agents, antihypertensive agents), have a narrow efficacy/toxicity ratio (e.g. digoxin, warfarin) and/or are known to induce or inhibit the cytochrome P450 (CYP) system (e.g. rifampicin [rifampin], cimetidine, fluconazole, etc.).

1. Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions Between Antihyperglycaemic Agents

In view of the growing complexity of choice in the treatment of type 2 diabetes, it is important to consider drug-drug interactions between various antihyperglycaemic agents. As the four classes of antidiabetic drugs that are currently available (sulphonylureas or meglitinide derivatives, biguanides, α-glucosidase inhibitors and thiazolidinediones) have different modes and sites of action, they may be combined to further improve glycaemic control in most patients[3-6] (figure 1). Each class of antihyperglycaemic agents has its own efficacy and safety profile[17] and combination therapy should ideally improve the efficacy in controlling fasting and post-prandial blood glucose levels without worsening the tolerability profile of the pharmacological intervention. The additive nature of the response offers the potential to combine drugs in an attempt to reach glycaemic goals that become more strict over time.[6]

The classical sulphonylurea and metformin combination that was very popular for many decades is now challenged by other combinations that include thiazolidinediones (usually combined with either a sulphonylurea or metformin) or α-glucosidase inhibitors (again generally combined with a sulphonylurea or metformin). Because of the greater number of pharmacological classes available to treat diabetes (thiazolidinediones, meglitinide derivatives), the variety of drug combinations in diabetic patients is currently increasing in an impressive manner. This article will first focus on the most prescribed dual combinations that have been tested in randomised clinical trials and/or in pharmacokinetics interaction studies. The use of a triple combination, including metformin, a sulphonylurea and a thiazolidinedione, is attractive.[18,19] Therefore, this first section will end by briefly describing both the efficacy and safety of this triple pharmacological combination in the management of type 2 diabetes.

1.1 Sulphonylurea-Metformin Combination

The sulphonylureas were the first oral drugs for type 2 diabetes treatment.[20] They act at the pancreatic B-cell membrane to cause closure of adenosine triphosphate (ATP)-sensitive potassium channels, which leads to an enhanced insulin secretion. They are commonly prescribed alone or in combination in order to reach glucose control targets.[21] Metformin is a biguanide compound that exerts a complex metabolic effect, essentially a reduction of hepatic glucose production, that results in increased action of insulin and antihyperglycaemic activity.[22,23] Currently, metformin is considered to be the first-choice drug in obese patients with type 2 diabetes and is the first adjunctive drug to be added to sulphonylurea therapy in the case of monotherapy failure.[24] Numerous studies have demonstrated that therapy with metformin and sulphonylurea exerts an antihyperglycaemic effect that is at least additive, and combined administration does not increase the risk of adverse effects associated with either agent given alone.[21,25] Most of the published studies have investigated the combination of metformin with the leading sulphonylurea in the market, glibenclamide. However, more recent studies have also confirmed the efficacy of combining metformin with the more recent sulphonylureas, gliclazide[26,27] and glimepiride.[28-30] In a large randomised, parallel-group, multicentre study in patients with type 2 diabetes, combination therapy with glimepiride plus metformin was significantly more effective than monotherapy with either agent in terms of glycosylated haemoglobin (HbA_{1c}) level reduction.[31] In the recent head-to-head, large-scale comparative European GUIDE (Glucose Control in Type 2 Diabetes: Diamicron Versus Glimepiride) study, gliclazide modified release 30–120mg daily and glimepiride 1–6mg daily were shown to be effective, either alone or in combination with metformin (57% of the population), with a 1.0–1.2% similar decrease of HbA_{1c} levels in patients receiving glimepiride and those receiving gliclazide. Approximately 50% fewer confirmed mild hypoglycaemic episodes were observed with gliclazide modified release than with glimepiride, whereas the frequency of severe hypoglycaemic episodes was low and comparable between treatments.[32]

In some countries, metformin has recently become available in single-tablet combination products also containing a sulphonylurea (glibenclamide or glipizide).[24] In a randomised, crossover study in 28 healthy subjects, a combination metformin/glibenclamide tablet demonstrated similar pharmacokinetics to the reference metformin and glibenclamide components, with no interference due to concomitant food intake.[33] Three large randomised, parallel-group, controlled trials recently compared the efficacy and tolerability of fixed-dose metformin/glibenclamide combinations with metformin monotherapy and glibenclamide monotherapy.[34-36] All of these 16–20 week duration studies demonstrated that metformin/glibenclamide combination tablets provide significant improvements in HbA_{1c} levels compared with metformin or glibenclamide monotherapy. As expected, the incidence of hypoglycaemia was greater in the groups receiving glibenclamide (alone or in combination), while the incidence of gastrointestinal adverse effects was higher in the groups receiving metformin (alone or in combination). Both the efficacy and safety of the fixed combination were confirmed in a 52-week open-label extension study.[37] Similarly, a randomised, double-blind, parallel-group, multicentre trial compared monotherapy with metformin or glipizide, and the combination metformin/glipizide

tablet for second-line treatment in patients with type 2 diabetes that was inadequately controlled by sulphonylurea therapy.[38] The efficacy of a combined metformin/glipizide tablet was superior to that of monotherapy with either agent and such treatment appeared to be well tolerated.

Even if metformin and sulphonylureas are the most often used combination in the treatment of type 2 diabetes, some concern has been raised about the safety of this common combination therapy. The UKPDS (UK Prospective Diabetes Study) showed significantly increased mortality among patients receiving a combination of a sulphonylurea and metformin when compared with those treated with sulphonylurea only.[39] Such astonishing findings caused much controversy; some diabetologists thought that the difference was only due to statistical problems resulting from between-group imbalance because of a rather low number of subjects receiving the combined therapy, whereas others considered that the combination may indeed be associated with a higher mortality risk for still unknown reasons.[40] Since these initial observations in the UKPDS, at least three epidemiological studies have confirmed these results, with the increased mortality risk persisting even after adjustment for most important potential confounders.[41-43] Therefore, all-cause and cause-specific mortality rates in diabetic patients treated with combinations of sulphonylureas and metformin deserve to be further investigated in larger samples of patients. The mechanisms involved in this possible increase in mortality also require careful study. Interaction of sulphonylureas with ATP-dependent K channels (K_{ATP}) in the myocardium has been suggested as playing a role, as this could lead to an impairment of physiological responses to ischaemia (see section 2.1.3). However, the reason why this effect might be potentiated by metformin remains obscure. This hypothetical harmful adverse effect, together with the well known progressive metabolic deterioration leading to insulin requirement observed with this combination (also shown in the UKPDS),[39] have stimulated the search for new antihyperglycaemic combinations that may have better efficacy and safety.

1.2 Sulphonylurea-Thiazolidinedione Combination

Thiazolidinediones are now widely used as part of antidiabetic treatments.[44-46] These agents act by targeting insulin resistance instead of stimulating insulin secretion. They interact with the gamma type of the peroxisome proliferator-activated receptor (PPAR)-γ. PPAR-γ, a member of the nuclear receptor subfamily, stimulates gene expression of the proteins involved in glucose metabolism.[47] This results in an increase in insulin sensitivity in skeletal muscle and adipose and liver tissues. Since the withdrawal of the first thiazolidinedione compound, troglitazone, because of hepatotoxicity,[48] two further thiazolidinediones have now been commercialised and are widely prescribed, i.e. pioglitazone[49,50] and rosiglitazone.[51,52] Unlike the sulphonylureas and metformin, thiazolidinediones are not used commonly as first-line therapy.[45,46] However, there is considerable evidence for the incorporation of thiazolidinediones into combination regimens, particularly in patients who do not achieve glycaemic goals with conventional regimens.

When pioglitazone was added to sulphonylurea therapy in type 2 diabetic patients inadequately controlled by monotherapy, HbA_{1c} levels were reduced by 0.65–1.7% from baseline, with the largest decline being reached at a dosage of 45mg daily.[51] In all studies employing pioglitazone 30mg daily added to sulphonylurea therapy, a significant mean decrease in HbA_{1c} level of 1.2% was observed.[53-55] In patients with type 2 diabetes inadequately controlled by near maximal doses of a sulphonylurea alone, adding rosiglitazone 4mg daily leads to enhanced and sustained glycaemic control, with a mean reduction in HbA_{1c} level of 1% at 6 months compared with the control group.[56] Similarly, in a randomised, open-label, 26-week international study, the addition of rosiglitazone 2mg twice daily to existing sulphonylurea therapy in patients with type 2 diabetes resulted in a significant reduction in HbA_{1c} (−1.13%, $p < 0.001$), while the mean HbA_{1c} level remained essentially unchanged in the control group.[57] A 12-month randomised, controlled trial demonstrated that the combination of either pioglitazone 15mg daily or rosiglitazone 4mg daily with glimepiride 2mg twice daily significantly improved

glycaemic control, with a reduction in HbA_{1c} level of 1.3% after 12 months.[58] In all these studies, the improvement in glycaemic control was achieved without exacerbation of the severe hypoglycaemia that is associated with sulphonylurea monotherapy, although the incidence of mild hypoglycaemic episodes was generally higher with combination therapy.

The administration of pioglitazone 30mg daily for 7 days had no significant effect (relative to baseline) on the pharmacokinetic characteristics of glibenclamide 5–10mg daily or gliclazide 160mg daily in a Japanese study in nine patients with type 2 diabetes.[49] The extent of protein binding of the two sulphonylureas was not affected by the presence of pioglitazone.

1.3 Combination of Metformin-Thiazolidinedione

Metformin, which primarily acts on the liver, and a thiazolidinedione, which primarily acts on the peripheral tissues (adipose tissue and skeletal muscles) may exert additive effects as remarkably demonstrated with the initial thiazolidinedione, troglitazone.[59] Since this pilot trial, the clinical efficacy and safety of combining metformin with either pioglitazone[60] or rosiglitazone[61,62] have been evaluated in several large randomised, clinical trials performed in patients with type 2 diabetes.

In a 16-week randomised, double-blind, parallel-group trial, patients with poorly controlled type 2 diabetes received either metformin plus pioglitazone 30 mg/day or metformin plus placebo.[60] The group that received metformin plus piogitazone had a mean decrease in HbA_{1c} level of 0.83% relative to placebo group. In a 72-week, open-label, extension phase, in which pioglitazone could be titrated to 45 mg/day, the group receiving metformin plus pioglitazone had a mean 1.36% decrease in HbA_{1c} level from the original baseline value. The combination also provided positive effects on triglyceride and high-density lipoprotein (HDL) cholesterol levels. Rates of adverse events were similar between groups, and most events were mild or moderate.

In a large 6-month, randomised, double-blind, placebo-controlled study, rosiglitazone was added at dosages of 4mg or 8mg daily to metformin therapy in patients with type 2 diabetes inadequately controlled by metformin 2.5g daily.[61] Clinically meaningful improvements in glycaemia were observed, with mean reductions in HbA_{1c} levels of 1.0% and 1.2% after addition of rosiglitazone 4 and 8 mg/day, respectively. Interestingly, such an improvement was observed despite the fact that metformin was used at near-maximal doses. This improvement was more pronounced in the obese population. These observations suggest that rosiglitazone has a complementary mechanism of action to metformin. In addition, the improvement was achieved without exacerbation of the gastrointestinal disturbances associated with metformin monotherapy.

A 26-week, randomised, placebo-controlled, multicentre trial conducted in Mexico compared the efficacy of metformin 2.5 g/day plus rosiglitazone 4 mg/day, metformin 2.5 g/day plus rosiglitazone 8 mg/day and metformin 2.5 g/day plus placebo, taken twice daily in divided doses.[62] At the end of the study, HbA_{1c} values had decreased by 0.7% in the group receiving low-dose rosiglitazone and by 1.2% in the group receiving high-dose rosiglitazone, compared with an increase of 0.3% in the group receiving metformin plus placebo.

A few studies have compared the efficacy of the metformin-thiazolidinedione combination with that of the sulphonylurea-thiazolidinedione combination in patients with type 2 diabetes.[63,64] The Quartet study group assessed the 1-year efficacy and safety of the addition of pioglitazone (15–45mg daily) or metformin (850–2550mg daily) to existing sulphonylurea therapy in patients with inadequately controlled type 2 diabetes.[64] HbA_{1c} levels were reduced by 1.20% in the sulphonylurea plus pioglitazone group and by 1.36% in the sulphonylurea plus metformin group (there was no significant difference between the two therapeutic modalities). Despite clinically equivalent improvements in glycaemic control, the addition of thiazolidinedione rather than metformin to suphonylurea therapy resulted in a reduction in the urinary albumin-creatinine ratio and significantly greater improvements in triglyceride and HDL cholesterol levels; however, this was associated with a small but significant rise in intermediate low-density lipoprotein (LDL) cholesterol levels. The authors concluded that sulphonylurea plus pioglitazone is an effective

and well tolerated combination regimen that may provide additional beneficial effects for patients with type 2 diabetes.

One study evaluated the effects of coadministration of metformin and rosiglitazone on the pharmacokinetics of either agent in healthy volunteers.[65] Subjects received metformin (500mg every 12 hours), rosigitazone (2mg every 12 hours), or a combination of both, for 4 days. Coadministration had no significant effects on the steady-state pharmacokinetics of metformin or rosiglitazone, which suggests that both compounds can be safely co-prescribed in order to reach glucose targets. In some countries, metformin has recently become available in single-tablet products containing rosiglitazone.

1.4 Sulphonylurea-α-Glucosidase Inhibitor Combination

α-Glucosidase inhibitors are pharmacological agents that competitively and reversibly inhibit the α-glucosidase enzymes in the brush border of the small intestine mucosa. Thereby, they prevent the hydrolysis of complex carbohydrates, retard the absorption of glucose and limit postprandial hyperglycaemia. Acarbose is the most extensively investigated and widely prescribed α-glucosidase inhibitor,[66-68] while miglitol[69] and voglibose[70] are two other compounds belonging to this pharmacological class that are available only in a limited number of countries (voglibose is only available in Japan).

Although acarbose is an effective monotherapy for type 2 diabetes,[71] its distinct and complementary mechanism of action induces a further improvement in glycaemic control when it is used in combination with other antidiabetic agents.[72] The effects of adding acarbose (maximum dosage of 100mg three times daily) versus placebo to an existing treatment regimen were investigated in a subset of patients enrolled in the UKPDS.[73] In patients who remained on their allocated therapy for 3 years, the median HbA_{1c} value was 0.5% lower in the acarbose group than in the placebo group ($p < 0.0001$). Importantly, acarbose therapy improved glycaemia, regardless of the previous treatment regimen. In another open-label, clinical trial, glycaemic control was improved when acarbose was added to a failing sulphonylurea regimen.[74] Finally, in a small study in overweight sulphonylurea-treated type 2 diabetic patients with poor metabolic control, the administration of acarbose alone produced equivalent reductions in HbA_{1c} levels as the combination acarbose plus metformin.[75]

Several studies have investigated the concomitant use of miglitol with other oral antidiabetic agents in patients with type 2 diabetes in whom glycaemic control was suboptimal despite dietary and pharmacological intervention.[69] Most of these studies evaluated the adjuvant use of miglitol in combination with sulphonylureas.[76,77] With concomitant miglitol 50mg and 100mg three times daily compared with placebo, there was a significant reduction from baseline in HbA_{1c}, fasting plasma glucose and postprandial plasma glucose levels. Concomitant therapy with miglitol and sulphonylurea agents reduced fasting serum triglyceride levels significantly compared with placebo and sulphonylurea agents. Although the overall incidence of adverse events increased when miglitol was combined with sulphonylurea agents compared with miglitol as monotherapy, the incidence of adverse events (essentially gastrointestinal effects) attributable to miglitol as part of a combination regimen was similar to that observed with miglitol alone.[69] A Japanese study showed that combination therapy with voglibose and a sulphonylurea agent prolongs the duration of good glycaemic control compared with a sulphonylurea alone in patients with type 2 diabetes.[78]

Potential drug-drug pharmacokinetic interactions have been investigated between glibenclamide and the three available α-glucosidase inhibitors: acarbose, miglitol and voglibose. Gérard et al.[79] did not observe any significant alteration of glibenclamide pharmacokinetics in acarbose-treated type 2 diabetic patients. In this study, a single dose of glibenclamide 5mg was administered to 6 patients immediately before a standardised breakfast, following 1 week of treatment with either placebo or acarbose 100mg three times daily, received in a randomised, crossover sequence. Acarbose had no effect on glibenclamide pharmacokinetics, but induced a significant improvement in the blood glucose profile together with a significant reduction in post-meal plasma insulin levels. In contrast, slight modifications of the pharmacokinetic parameters of gliben-

clamide were observed after ingestion of miglitol in six healthy volunteers.[80] In a double-blind, crossover trial, each subject was randomly allocated to take either miglitol (50mg three times daily during the first 3 days and 100mg three times daily during the last 4 days) or placebo during two consecutive 7-day periods.[81] At day 7 and day 14 of the study, the participants, who had fasted overnight, ingested glibenclamide 5mg together with either miglitol 100mg or placebo with the first bite of a standardised breakfast. The time to maximum concentration (t_{max}) and maximum concentration (C_{max}) of serum glibenclamide levels were similar after miglitol and placebo. However, the glibenclamide area under the concentration-time curve (AUC) was 33% ($p < 0.05$) lower after miglitol was administered than after placebo. Finally, a study was performed to investigate whether or not voglibose modifies the pharmacokinetics of glibenclamide (single dose of 1.75mg) and the glibenclamide-induced decrease in fasting serum glucose levels. The concentration-time course of glibenclamide with concomitant voglibose administration (5mg three times daily for 8 days) was similar to that with placebo. The glibenclamide-induced decrease in fasting serum glucose level was similarly independent of placebo or voglibose coadministration. As voglibose did not interact with glibenclamide on a pharmacokinetic level, concomitant treatment was well tolerated and has been proven to be safe for further clinical use.

1.5 Metformin-α-Glucosidase Inhibitor Combination

The absorption of metformin occurs mainly from the small intestine and it has been shown that high concentrations (10–100 times plasma levels) accumulate in the walls of the gastrointestinal tract.[82] Therefore, possible pharmacokinetic interferences with drugs acting on the intestinal wall, such as α-glucosidase inhibitors, are not excluded. It has been demonstrated in six healthy individuals that acarbose (100mg) induced moderate but significant reductions (−35%, $p < 0.05$) in the C_{max} and AUC of metformin that had been ingested as two 500mg tablets with a standardised breakfast.[83] However, this pharmacokinetic interaction does not exclude the possibility that such a combination may be useful in the management of patients with type 2 diabetes.

Acarbose therapy effectively improved glycaemia in overweight patients with type 2 diabetes inadequately controlled by metformin. The clinical efficacy and safety of the combination of acarbose with metformin has been evaluated in several randomised, clinical trials.[75,84-86] In a 30-week US study, mean HbA_{1c} level was reduced by 0.57% from baseline in the metformin plus acarbose group and increased by 0.08% in the metformin plus placebo group.[84] The differences in metabolic control were even greater in a 6-month French study (−0.7% in the metformin plus acarbose group vs +0.2% in the metformin plus placebo group; $p = 0.0001$)[85] and in a 24-week study performed in Australia and New Zealand (difference in HbA_{1c} level between acarbose and placebo: 1.02%, $p = 0.0001$).[86] Interestingly, the incidence of hypoglycaemia was not higher with the combination therapy, despite the better metabolic control. As expected, in all of these trials a greater proportion of the metformin plus acarbose group experienced gastrointestinal adverse effects compared with the metformin plus placebo group.

The combination of metformin and miglitol was studied in a 36-week randomised, double-blind, placebo-controlled trial.[87] The treatment arms were metformin 500mg three times daily; miglitol titrated to 100mg three times daily; metformin plus miglitol at the aforementioned doses; and placebo. Mean changes from baseline in HbA_{1c} values were −0.85%, +0.02%, −1.39% and +0.38% for metformin, miglitol, metformin plus miglitol and placebo, respectively. The mean change in HbA_{1c} level was significantly greater in the group receiving metformin plus miglitol compared with the groups receiving either monotherapy. Thus, miglitol can be combined effectively with metformin therapy to give significantly greater reductions in HbA_{1c} and postprandial plasma glucose levels than metformin alone, with a good safety profile.

1.6 Thiazolidinedione-α-Glucosidase Inhibitor Combination

Studies that have investigated the effects of the combination of a thiazolidinedione with an α-glucosidase inhibitor are sparse, despite the fact

that an early clinical trial reported the efficacy and safety of combining troglitazone and acarbose.[88]

The effect of acarbose (100mg per day for 7 days) on the pharmacokinetics of rosiglitazone (a single 8mg dose) has been studied in healthy volunteers.[89] Rosiglitazone absorption, as assessed using the C_{max} and t_{max}, was unaffected by acarbose. However, the AUC_{∞} was on average 12% lower during rosiglitazone plus acarbose coadministration and was accompanied by an approximate 1-hour reduction in terminal elimination half-life. This small decrease in AUC appears to be due to an alteration in the systemic clearance of rosiglitazone and not changes in absorption. These observed changes are not likely to be clinically relevant and coadministration of rosiglitazone and acarbose was well tolerated.

An open-label study evaluated the efficacy, safety and clinical profile of pioglitazone (30mg once daily) taken orally for 16 weeks in patients whose type 2 diabetes was poorly controlled with an α-glucosidase inhibitor alone or taken in combination with sulphonylurea.[90] The α-glucosidase inhibitors in use were acarbose 300mg daily in nine patients and voglibose 0.6mg daily in ten patients. There were significant reductions in HbA_{1c}, fasting plasma glucose and postprandial plasma glucose levels at the end of the study compared with baseline. Adverse signs and symptoms associated included two episodes of oedema and two episodes of hypoglycaemia-like reaction. Another Japanese study evaluated the efficacy of adding pioglitazone 30mg daily to the therapy of patients with type 2 diabetes whose glycaemic control was poor on therapy of an α-glucosidase inhibitor alone or in combination with a sulphonylurea.[91] Again, the addition of pioglitazone resulted in a significant decrease in HbA_{1c} and the treatment was generally well tolerated.

1.7 Meglitinide Derivatives Combined with Metformin

Meglitinide derivatives are non-sulphonylurea agents that are insulin secretagogues and have a similar mechanism of action to the sulphonylureas, but with different pharmacokinetic and pharmacodynamic properties.[92] Repaglinide[93,94] and nateglinide[95-97] belong to this new class of oral agents with a specific action on early-phase insulin release, thus targeting postprandial hyperglycaemia, and a shorter elimination half-life and duration of action, thus reducing the risk of late hypoglycaemia. The meglitinide derivatives do not further stimulate insulin release in patients who have already been treated with maximal doses of sulphonylurea drugs. Thus, the meglitinides offer an alternative to sulphonylurea management.[20,92] These drugs are ideally suited for use in combination with metformin or the thiazolidinediones.[98]

Repaglinide is licensed for use as monotherapy and in combination with metformin or a thiazolidinedione.[93,94,98] Clinical studies have shown repaglinide plus metformin to be an effective combination.[99] Patients with type 2 diabetes that was inadequately controlled with metformin alone were treated with a continuation of metformin alone, repaglinide alone or the combination of metformin and repaglinide for 3 months. HbA_{1c} levels decreased by 1.4% in the combination therapy group, while glycaemic control did not improve in either monotherapy arm.

Nateglinide, a *d*-phenylalanine derivative, has been launched for use in combination therapy in patients with type 2 diabetes that was inadequately controlled by metformin alone.[95-97] In targeting the defect in early-phase insulin release, nateglinide works well when given in combination with agents of a complementary mechanism of action. When nateglinide (120mg, three times daily before meals) was coadministered for 1 day in patients with type 2 diabetes mellitus who had been receiving metformin 500mg three times daily for 3 weeks, no significant alterations in the pharmacokinetics of either agent were seen.[100] In order to investigate the clinical effectiveness of nateglinide in combination with metformin, a total of 701 patients with type 2 diabetes were randomly assigned to one of four treatment groups: placebo, nateglinide monotherapy, metformin monotherapy and nateglinide plus metformin combination therapy.[101] At the end of the 24-week study period, combination therapy resulted in significantly lower fasting and post-meal plasma glucose levels and lower HbA_{1c} values. The metformin and nateglinide combination had additive effects, reducing HbA_{1c} levels by 1.4% from baseline compared with 0.8% for monotherapy with metformin and

0.5% for nateglinide monotherapy. The highest reported incidence of hypoglycaemia occurred in the group receiving combination therapy (26%), with little difference between the metformin and nateglinide monotherapy groups (10 and 13%, respectively). However, there were no serious hypoglycaemic events and the numbers of patients who experienced any episode of hypoglycaemia that was confirmed by plasma glucose measurement were low. These observations of an additive effect on blood glucose control of the metformin-nateglinide combination were confirmed in a European multicentre study.[102] HbA_{1c} levels were significantly reduced with nateglinide 60mg and 120mg plus metformin compared with metformin alone (−0.36% and −0.59%, respectively), with low rates of hypoglycaemia. A theoretical model predicted that combination therapy with nateglinide and metformin, compared with metformin alone, would reduce the frequency of complications and thus, reduce treatment costs.[103]

Only one randomised, open-label, parallel-group, multicentre trial has been conducted to compare the efficacy and safety of repaglinide versus nateglinide, when used in a combination regimen with metformin (1g twice daily) for the treatment of type 2 diabetes.[104] The addition of repaglinide (median final dosage of 5.0mg daily) to metformin therapy resulted in reductions in HbA_{1c} levels (−1.28 vs −0.67%, $p < 0.001$) and fasting plasma glucose values that were significantly greater than the reductions observed for addition of nateglinide (median final dosage of 360mg daily). Safety assessments were comparable for the two regimens.

1.8 Meglitinide Derivatives Combined with Thiazolidinediones

As an alternative to a combination with metformin, meglitinide derivatives could also prove effective when used in combination with a thiazolidinedione. Initially, repaglinide[105] and nateglinide[106] combined with troglitazone showed an additive effect that was highly effective in reducing HbA_{1c} levels. A randomised, open-label, parallel-group, multicentre study compared the efficacy and safety of combination therapy with repaglinide plus pioglitazone (30mg daily) to repaglinide or pioglitazone alone over 24 weeks of treatment in patients with type 2 diabetes who had previously failed to respond to oral antidiabetic monotherapy.[107] The combination therapy showed better efficacy than monotherapy, with greater reductions in HbA_{1c} levels (−1.76% vs −0.18% for repaglinide and +0.32% for pioglitazone) and acceptable tolerability.

No alterations in the pharmacokinetics of either agent were observed when nateglinide 120mg was administered before meals for 1 day in combination with glibenclamide 10mg that had been given once daily for 3 weeks (a combination that is not recommended in clinical practice) or when it was administered in a similar manner to patients who had been receiving troglitazone (a CYP3A4 inducer) 600mg once daily for 3 weeks.[97]

1.9 Triple Therapy Metformin-Sulphonylurea-Thiazolidinedione

Clinical trials with triple oral therapy are scarce and have essentially combined metformin, a sulphonylurea and a thiazolidinedione.[18,19] Initial studies used troglitazone and reported promising results.[108,109] These observations were confirmed with either pioglitazone[110] or rosiglitazone[111] in combination with a sulphonylurea and metformin. Such triple therapy appears to be efficacious and safe, even in the long-term,[112] and feasible.[113] However, more data are required from larger populations followed on a long-term basis.[18] The use of fixed combination of metformin plus glibenclamide or metformin plus thiazolidinedione will facilitate the use of such triple therapy in the near future.[114] The positive results reported with the triple therapy provide an alternative to switching to insulin treatment when two oral agents fail to control type 2 diabetes.[19] Two recent head-to-head studies compared the safety and efficacy of adding insulin or a thiazolidinedione to therapy in the case of failure with the dual classical therapy, sulphonylurea plus metformin.[110,111] The glycaemic benefits were equivalent with the two therapeutic strategies, whatever the mode of insulin administration, i.e. bedtime insulin suspension isophane (neutral protamine Hagedorn [NPH] insulin)[110] or twice daily 70/30 insulin.[115] Thus, available data suggest that adding either a thiazolidinedione or insulin to sulphonylurea/metformin therapy is appropriate. Well designed studies, such as those that have been

reported recently, may be slowly moving treatment from judgments based on opinion to treatment based on medical facts.[19]

2. Drug-Drug Interactions Between Antihyperglycaemic Agents and Other Pharmacological Compounds

Drug-drug interactions between antihyperglycaemic agents and other pharmacological compounds may be two-sided: on the one hand, antihyperglycaemic agents may influence the plasma concentrations of other coadministered drugs, a pharmacokinetic interaction that is mainly of clinical relevance when it concerns drugs with a low toxicity/efficacy ratio such as digoxin or warfarin; on the other hand, other coadministered pharmacological compounds may influence the plasma concentrations of antihyperglycaemic agents.[15,116] In the case of simultaneous administration of an inhibitor of the CYP system, the main concern is the risk of potentiating hypoglycaemia, a clinical issue that is most frequently observed with insulin secretagogues such as sulphonylureas, whereas it is rather exceptional with insulin sensitisers (metformin, thiazolidinediones) and almost nonexistent with α-glucosidase inhibitors.[117,118] The risk of hypoglycaemia due to drug-drug interaction is even more important in case of renal failure, a condition that is frequently present in diabetic patients and that may lead to an accumulation of the native compound or active metabolite.[119] In the case of simultaneous administration of a CYP inducer, the potential risk is deterioration of glycaemic control that will require dose adjustment of the antihyperglycaemic agent or addition of another glucose-lowering drug.

Several pharmacological classes are of particular interest to study in patients with type 2 diabetes. This is the case for drugs that are prescribed to treat comorbidities frequently associated with type 2 diabetes, such as lipid-lowering drugs,[120] antihypertensive agents[121] or, in general, compounds used for the prevention and treatment of coronary heart disease. Alternatively, it may also be the case for drugs that could induce metabolic disturbances that require the prescription of oral antidiabetic drugs, e.g. antiretroviral drugs[122] or antipsychotic agents, especially those of the second-generation that are also called atypical antipsychotics.[123,124]

2.1 Oral Antihyperglycaemic Agents and Other Drugs for Cardiovascular Disease Prevention

2.1.1 Lipid-Lowering Agents and Safety Profile

Recent evidence indicates that effective treatment of dyslipidaemia in patients with diabetes reduces adverse macrovascular outcomes. Large studies of lipid-modifying drugs have shown that diabetic patients clearly benefit from HMG-CoA reductase inhibitor (statin) therapy.[125,126] A recent clinical guideline from the American College of Physicians recommends lipid-lowering therapy with a statin in almost all patients with type 2 diabetes.[127] Fibric acid derivatives (fibrates) are also widely prescribed in diabetic patients because these drugs have a positive impact on diabetic dyslipidaemia, i.e. high triglyceride levels associated with low HDL cholesterol levels, commonly found in overweight patients with type 2 diabetes.[128] However, little is known about the frequency of drug-drug interactions between cholesterol-lowering drugs and the various classes of antidiabetic agents.

HMG-CoA Reductase Inhibitors

The statins are well tolerated apart from two uncommon but potentially serious adverse effects; asymptomatic elevation of liver enzyme levels and skeletal muscle abnormalities, which range from benign myalgias to life-threatening rhabdomyolysis. Adverse effects with statins are frequently associated with drug interactions because of their use in patients who are likely to be exposed to polypharmacy. This may be the case in type 2 diabetic patients. Drug interactions involving statins may have either a pharmacodynamic or pharmacokinetic basis, or both. The CYP enzyme system plays an important part in the metabolism of most statins (except pravastatin), leading to clinically relevant interactions with other agents.[120,129,130]

An early study showed that lovastatin does not affect serum chlorpropamide concentrations and diabetes control in patients with type 2 diabetes.[131] However, single and multiple coadministration of fluvastatin 40mg or simvastatin 20mg increased the mean C_{max} and AUC of glibenclamide by approximately 20%.[132] The pharmacokinetics of tolbutamide were influenced to only a minor extent. Con-

versely, fluvastatin concentration-time profiles were unaffected by tolbutamide or glibenclamide coadministration. The pharmacokinetic interactions between fluvastatin or simvastatin and tolbutamide and glibenclamide were not associated with clinically relevant changes in blood glucose and insulin levels and are not, therefore, considered to be relevant in therapeutic practice. Concomitant treatment with repaglinide and simvastatin, a CYP3A4 substrate, only minimally altered the mean repaglinide AUC (+2%) and C_{max} (+27%).[133] However, the incidence of adverse effects increased with coadministration of the two drugs compared with repaglinide treatment alone.

Statins can be used concomitantly with thiazolidinediones to improve the dyslipidaemic profile associated with insulin resistance and to improve the poor cardiovascular prognosis of patients with type 2 diabetes. As both statins[130] and thiazolidinediones[134] are metabolised via the CYP system, pharmacokinetic drug-drug interactions may occur. Consequently, the interaction potential between the two pharmacological classes needs to be known, especially as cerivastatin and troglitazone were recently withdrawn from the market for safety problems partly linked to interferences with drug metabolism.[135]

Troglitazone was a CYP3A4 isoenzyme inducer known to decrease the plasma concentrations of drugs metabolised by CYP3A4.[134,136] Atorvastatin is a known substrate of the CYP3A4 pathway. A study retrospectively reviewed a small number of medical records of patients who received concomitant troglitazone and atorvastatin therapy.[137] The increase in LDL-cholesterol (+23%) and triglyceride (+21%) levels on atorvastatin and troglitazone combination therapy compared with atorvastatin monotherapy may be suggestive of a drug interaction. One study investigated the potential pharmacokinetic interaction between troglitazone and simvastatin in healthy subjects.[138] Troglitazone diminished the C_{max} of simvastatin by 30% and the AUC of simvastatin by 40%, whereas simvastatin caused a small but clinically insignificant increase (approximately 25%) in the C_{max} for troglitazone. A study examined the US FDA database to determine the frequency of adverse events in patients taking both an statin and an antidiabetic medication.[139] This study found that patients who had an adverse event while taking atorvastatin were approximately 4-fold more likely to also be taking a thiazolidinedione (troglitazone in 95% of patients at the time of the survey) than patients reporting an adverse event while taking simvastatin, despite equivalent proportions of both patient groups concomitantly taking other antidiabetic medications. These adverse events occurred in patients taking relatively small doses of each medication, and after several months of concomitant therapy. According to the authors, these findings raise serious and previously unrecognised concerns for potential adverse drug-drug interactions in patients taking these two widely used classes of medications. However, as the most common adverse event reported to the FDA in patients taking this combination was hepatotoxicity, an adverse effect specific to troglitazone,[48] this concern may not be found with the new thiazolidinediones, pioglitazone and rosiglitazone. The same authors recently reported data with rosiglitazone and pioglitazone using the same methodology.[140] Again, it was observed that atorvastatin-associated adverse event reports were 3.1 times more likely to list rosiglitazone or pioglitazone as a concomitant medication compared with simvastatin-associated adverse event reports. In this more recent survey, muscle toxicity was the most common adverse event noted. The exact mechanism for this statin-thiazolidinedione interaction is not well known, although a potential drug-drug interaction via CYP3A4 is suspected.[140]

Caution is recommended when combining a statin whose metabolism is dependent on CYP3A4 (such as simvastatin or atorvastatin) with a drug that inhibits CYP3A4.[130] Rosiglitazone is metabolised via N-demethylation and hydroxylation and has no effect on drugs metabolised by liver cytochrome enzymes,[141] whereas pioglitazone is metabolised via the CYP2C8 and CYP3A4 pathways.[44,142] Consequently, pioglitazone may alter the metabolism of statins that are metabolised by the CYP3A4 pathway.

The effect of rosiglitazone in combination with atorvastatin was evaluated in patients with type 2 diabetes.[143] After 8 weeks of treatment with rosiglitazone 4mg twice daily, patients were randomised to receive rosiglitazone with atorvastatin 10 or 20 mg/day or placebo for 16 weeks. In the atorvastatin 10 and 20 mg/day treatment groups, LDL cholester-

ol decreased by 33% and 40%, respectively. The authors concluded that the combination of a thiazolidinedione and a statin effectively reduced LDL cholesterol in diabetic patients and was well tolerated.

If pioglitazone can induce CYP3A4, there is theoretically potential for an interaction with simvastatin. However, a pharmacokinetic study found that pioglitazone had no significant effect on the extent of the HMG-CoA reductase inhibitory activity of simvastatin.[138] According to some other observations, no evidence exists that pioglitazone induces the hepatic CYP isoform CYP3A4.[144] A clinical trial assessed the efficacy and tolerability of simvastatin 40mg compared with placebo in patients with type 2 diabetes who were receiving a stable dose of pioglitazone or rosiglitazone and had a baseline LDL cholesterol level of >100 mg/dL.[145] Simvastatin was an effective and generally well tolerated treatment for hyperlipidaemia when used in combination with thiazolidinedione therapy in patients with type 2 diabetes. No differences in safety profile were observed between simvastatin and placebo. Simvastatin had no additional impact on the adverse effects common to thiazolidinedione therapy and glycaemic control was unaffected, as evidenced by a lack of effect on HbA_{1c} levels and on glucose and insulin levels. Thus, simvastatin did not appear to have any detrimental effects on the insulin-sensitising activity of thiazolidinediones. Also, simvastatin recipients did not appear to have an increased incidence of liver or muscle toxicity. Finally, no clinically meaningful differences in adverse effects were observed between statin-treated patients taking pioglitazone and those taking rosiglitazone.

Fibric Acid Derivatives

Among fibric acid derivatives, gemfibrozil has been shown to be associated with potentially deleterious drug-drug interactions. For instance, it greatly increases plasma concentrations of cerivastatin by inhibiting CYP2C8 metabolism, a mechanism that may explain the higher incidence of rhabdomyolysis described with such a combination.[146] Gemfibrozil has a minor impact on the pharmacokinetics of the sulphonyurea compound glimepiride as it raises the mean AUC of glimepiride 1.2-fold.[147] This is markedly different from what has been recently reported with the meglitinide derivative, repaginide. A randomised, crossover study was designed to investigate possible interactions of gemfibrozil, itraconazole and their combination with repaglinide in healthy volunteers.[148] The AUC of repaglinide showed a 8-fold increase with gemfibrozil alone, a 1.4-fold increase with itraconazole alone and a 19.4-fold increase with the gemfibrozil-itraconazole combination. Thus, gemfibrozil considerably enhanced and prolonged the blood glucose-lowering effect of repaglinide. Clinicians should be aware of this potentially hazardous interaction between gemfibrozil and repaglinide. Concomitant use of gemfibrozil and repaglinide is best avoided. If the combination is considered necessary, the repaglinide dose should be greatly reduced to avoid hypoglycaemia and blood glucose levels should be carefully monitored.[148] In contrast to these observations with gemfibrozil, a three-phase, randomised, crossover, placebo-controlled study in healthy volunteers demonstrated that neither bezafibrate nor fenofibrate affects the pharmacokinetic variables (AUC, C_{max}, elimination half-life) of repaglinide.[149] Consequently, the blood-glucose lowering effect of repaglinide was not affected by bezafibrate or fenofibrate. These findings have important therapeutic consequences as many diabetic patients using oral antihyperglycaemic agents have hypertriglyceridaemia and low HDL cholesterol levels and may be prescribed fibric acid derivatives.

Rosiglitazone treatment does not impair the triglyceride-lowering activity of fibric acid derivatives in patients with type 2 diabetes.[150] However, as rosiglitazone is primarily metabolised by CYP2C8, its metabolism may also be impaired by gemfibrozil. A randomised, crossover study in healthy volunteers demonstrated that gemfibrozil (600mg twice daily for 4 days) shows a marked interaction with rosiglitazone (one single dose of 4mg). Indeed, gemfibrozil raised the mean plasma rosiglitazone AUC 2.3-fold and increased the elimination half-life of rosiglitazone from 3.6 hours to 7.6 hours.[151] Analysis of N-desmethyl metabolite concentrations suggested that gemfibrozil probably raises the plasma concentrations of rosiglitazone by inhibiting the CYP2C8-mediated biotransformation of rosiglitazone. Thus, coadministration of gemfibrozil or another potent inhibitor of CYP2C8 and

rosiglitazone could increase the efficacy of rosiglitazone but could also increase the risk of concentration-dependent adverse effects.

2.1.2 Antihypertensive Agents and the Risk of Hypoglycaemia

There is evidence that patients with type 2 diabetes also benefit from the vascular protective effects of antihypertensive agents, including diuretics, β-adrenoceptor antagonists (β-blockers), calcium channel antagonists, ACE inhibitors and angiotensin-receptor antagonists.[152] Antihypertensive agents may exert negative, neutral or even positive metabolic effects that may diversely affect the risk of developing type 2 diabetes.[153] High doses of thiazide-like diuretics or nonselective β-blockers may increase blood glucose levels and thus possibly worsen diabetes control by increasing insulin resistance and/or reducing insulin secretion. In contrast, β-blockers (by masking hypoglycaemic symptoms and blunting counter-regulation)[154] and ACE inhibitors (by improving insulin sensitivity)[155] have been associated with severe hypoglycaemia in several case reports. Calcium channel antagonists of the dihydropyridine family are considered to be metabolically neutral.[152] However, in a large survey of 13 559 elderly Medicaid enrolees with diabetes who were treated with insulin or sulphonylureas, there was no statistically significant increase or decrease in the risk of serious hypoglycaemia among patients receiving any class of antihypertensive agents compared with patients not taking antihypertensive drugs, after controlling for demographic characteristics and markers of comorbidity.[121] It was concluded that specific antihypertensive drug therapy has little impact on the risk of hypoglycaemia in older diabetic patients. Therapy should thus be chosen on the basis of other aspects of safety and effectiveness.[156]

ACE inhibitors have raised both interest, because of their potential of cardiovascular and renal protection[157] and concern, because of their potential for inducing hypoglycaemia.[155] ACE inhibitors can intensify the glucose-lowering effect of insulin and sulphonylureas. This observation has been observed in a few clinical cases[158] and studied systematically in regional pharmacovigilance centres.[155,159,160] A nested case-control study confirmed that ACE inhibitor therapy is associated with hospital admission for severe hypoglycaemia (in contrast to β-blockers or calcium antagonists) in diabetic patients.[161] In analyses that adjusted for potentially confounding variables, the association remained, with an odds ratio of 4.3. Separate analysis showed that the association between ACE inhibitor treatment and the risk of admission for hypoglycaemia was higher in patients receiving oral antihyperglycaemic drugs than those receiving insulin. However, the risk of severe hypoglycaemia in diabetic patients treated with ACE inhibitors or angiotensin-receptor antagonists appears to be very low and can be considered as negligible compared with the renal and cardiovascular benefits of this class in the diabetic population. Such a hypoglycaemic effect may result from improved insulin sensitivity and/or insulin secretion, which are changes that may involve many of the various biochemical and physiological mechanisms that are associated with the inhibition of the renin-angiotensin system.[162]

Both ACE inhibitors (or angiotensin-receptor antagonists) and thiazolidinediones exert beneficial vascular effects. It is likely that the concomitant use of a thiazolidinedione with an antihypertensive agent will potentiate the vascular benefits in patients with type 2 diabetes, although additional studies are needed to substantiate this. The DREAM (Diabetes REduction Approaches with ramipril and rosiglitazone Medication) trial, using the ACE inhibitor ramipril and the thiazolidinedione rosiglitazone, is designed to answer this important question.[163]

2.1.3 Sulphonylureas and Cardiovascular Interactions

Sulphonylureas and related K_{ATP} channel blockers stimulate insulin secretion from pancreatic B cells by binding to the sulphonylurea receptor (SUR) subunit of the K_{ATP} channels.[164] Related channels in cardiac and vascular smooth muscle are the targets for therapeutic K_{ATP} channel opening drugs, such as the antianginal agent nicorandil, but are blocked by a subgroup of the sulphonylureas and other related agents.[165] Sulphonylureas and meglitinide derivatives may exhibit differences in tissue specificity, as the drugs interact to varying degrees with different types of SUR. However, a recent study showed that there is no evidence that a SUR1-specific sulphonylurea, such as glimepiride, and a SUR1-nonspecific sulphonylurea, such as

gliclazide, have differential effects on arterial distensibility, endothelial function or vasodilator mechanisms in metformin-treated patients with type 2 diabetes.[166] Although K_{ATP} channels in cardiac and smooth muscle are largely closed under physiological conditions (but open during ischaemia), they are activated by antianginal agents such as nicorandil. Under these conditions, they may be inhibited by sulphonylureas that block SUR2-type K_{ATP} channels such as glibenclamide.[164] Although glibenclamide given as a single intravenous dose appears to antagonise the myocardial protective effect of nicorandil during acute ischaemia,[167] such antagonism has not been found during chronic oral treatment in diabetic patients.[168] Therefore, the real importance of K_{ATP}-channel specificity to avoid drug interferences remains a matter of debate in clinical practice.

2.2 Pharmacokinetic Drug-Drug Interactions

Drug interactions of clinical importance occur when the efficacy or toxicity of a medication is changed by administration of another substance. Pharmacokinetic interferences often occur as a result of a change in drug metabolism.[116] The CYP system oxidises a broad spectrum of drugs by a number of metabolic processes that can be enhanced or reduced by various compounds known as inducers (e.g. rifampicin) [table I] or inhibitors (e.g. antimycotic azole derivatives or macrolide antibacterials) [table II], respectively. CYP3A4 is involved in the metabolism of the majority of drugs in general (including meglitinide derivatives), although other CYP isoenzymes may also play a role, especially CYP2C9 for sulphonylureas and CYP2C8 for thiazolidinediones. The clinical importance of any drug interaction depends on factors that are drug-, patient- and administration-related.[169] Generally, a doubling (or greater increase) in plasma drug concentration has the potential for an enhanced adverse (or beneficial) drug response. Less pronounced pharmacokinetic interactions may still be clinically important for drugs with a steep concentration-response relationship or narrow therapeutic index, such as warfarin or digoxin (table III). Antihyperglycaemic agents acting through the release of insulin (sulphonylureas, meglitinide derivatives) are considered to have a narrow therapeutic index because they have a higher risk of hypoglycaemia.

Table I. Drug-drug interactions in healthy volunteers: effects of rifampicin (rifampin), a cytochrome P450 inducer, on the AUC of oral antihyperglycaemic agents metabolised in the liver. Results are expressed as the percentage increase in AUC with combination therapy compared with placebo

Drug	Rifampicin (%)	p-Value	Reference
Glibenclamide (glyburide)	−39	($p < 0.001$)	170
Glipizide	−22	($p < 0.05$)	170
Gliclazide	−70	($p < 0.001$)	171
Glimepiride	−34	($p < 0.001$)	172
Repaglinide	−57	($p < 0.001$)	173
Nateglinide	−24	($p < 0.001$)	174
Pioglitazone	NA		
Rosiglitazone	−65	($p < 0.001$)	175
	−54	($p < 0.001$)	176

AUC = area under the concentration-time curve; **NA** = no published data available.

2.2.1 Sulphonylureas

Most of the sulphonylureas are highly bound to plasma proteins and some of them have low clearance rates. Drug-drug interactions were initially and commonly assumed to be due to the displacement of the sulphonylurea from plasma proteins by the coadministered drug.[15,116] However, based on pharmacokinetic models of tolbutamide interactions, displacement from plasma proteins should have a small and only transient effect, if any, on insulin release from the pancreas. With further analysis and clinical studies, many of the drug interactions originally ascribed to changes in plasma protein binding are considered to result from inhibition of the enzymes responsible for metabolic clearance of the sulphonylurea compound. Indeed, most sulphonylurea drugs are extensively metabolised, increasing the potential for metabolism-based, drug-drug interactions. For instance, the classical first-generation sulphonylurea tolbutamide can be used to estimate the activity of the polymorphic CYP isoenzyme CYP2C9 and has been proposed for use in CYP2C9 phenotyping.[198] The effects of the CYP2C9 amino acid polymorphisms may be important for drug treatment with tolbutamide.[199] In a study performed in healthy volunteers, tolbutamide was confirmed as a substrate of the genetically polymorphic enzyme CYP2C9.[200] However, the pronounced differences in pharmacokinetics due to the amino acid variants did not significantly affect plasma insulin

Table II. Drug-drug interactions in healthy volunteers: effects of cytochrome P450 inhibitors on the AUC of new oral antihyperglycaemic agents metabolised by the liver. Results are expressed as percentage increase in AUC with combination therapy compared with placebo

Drug	Histamine H_2 receptor antagonists	Antifungals	Fibric acid derivatives	Other agents
Glimepiride	NA	+138%[177] (fluconazole)	+20%[147] (gemfibrozil)	+33%[177] (fluvoxamine)
Repaglinide	NS [178] (cimetidine)	+15%[133] (ketoconazole) +40%[148] (itraconazole)	+700%[148] (gemfibrozil)	+61%[179] (trimethoprim) +40%[180] (clarithromycin)
Nateglinide	NA	+48%[181] (fluconazole)	NA	28%[182] (sulfinpyrazone)
Pioglitazone	NA	NA	NA	NA
Rosiglitazone	NS[183] (ranitidine)	NA	+130%[150] (gemfibrozil)	+37%[176] (trimethoprim)

AUC = area under the curve; **NA** = no published data available; **NS** = no significant change.

and glucose levels in this population. Other sulphonylurea drugs (glibenclamide, glimepiride) also mainly utilise CYP2C9 for metabolism[201,202] and this isoenzyme is known to be of major importance in human drug metabolism.[203] CYP2C9 may be induced by HIV protease inhibitors, such as ritonavir and nelfinavir, with a resulting decrease in the antihyperglycaemic efficacy of the sulphonylurea.[122] Antiulcer H_2 histamine receptor antagonists (cimetidine, ranitidine) and antibacterial and antifungal azole-derivatives (ketoconazole, fluconazole) have been reported to precipitate hypoglycaemia when taken in combination with various sulphonylureas (i.e. glibenclamide, glipizide and gliclazide), the suggested mechanism being an inhibition of hepatic microsomal enzymes and thus sulphonylurea metabolism.[15]

Glibenclamide

Rifampicin, a rifamycin antibacterial, is a potent inducer of CYP enzymes and can greatly reduce the plasma concentrations and effects of numerous drugs.[204,205] Reports of the effects of rifampicin on the pharmacokinetics of second generation sulphonylureas are sparse. The blood glucose lowering effect of glibenclamide was significantly reduced by rifampicin, but unfortunately no pharmacokinetic data were obtained, in a study performed in India.[206] In healthy volunteers, rifampicin decreased the AUC of glibenclamide by 39% ($p < 0.001$) and the peak plasma concentration by 22% ($p = 0.01$).[170] The blood glucose decremental AUC and the maximum decrease in the blood glucose level were decreased by 44% ($p = 0.05$) and 36% ($p < 0.001$), respectively, when rifampin was coadministered with glibenclamide. Thus, it is probable that the blood glucose-lowering effect of glibenclamide is reduced during concomitant administration of rifampicin and glibenclamide in patients with type 2 diabetes. The mechanism underlying the interaction between rifampicin and glibenclamide is probably the induction of either CYP2C9[204,205] or P-glycoprotein,[207,208] or both.

Severe hypoglycaemia has been attributed to drug-drug interaction between glibenclamide and other drugs, especially antibacterials such as doxycycline,[209] or quinolones, including ciprofloxacin[210] and gatifloxacin.[211] Clinicians should consider these potential interactions in diabetic patients taking glibenclamide who require antibacterial therapy. Similarly, hypoglycaemia was also reported in diabetic patients treated with glibenclamide who were receiving an H_2 receptor antagonist such as cimetidine or ranitidine.[212,213] These adverse events may result from the inhibition of CYP2C9 and the concomitant reduction in sulphonylurea metabolism by the liver.

The possible occurrence of a kinetic interaction between ciclosporin A and glibenclamide was assessed by reviewing data of six post-transplant diabetic patients who received the two drugs concur-

Table III. Drug-drug interactions: effects of new oral antihyperglycaemic agents on the pharmacokinetics of digoxin and warfarin

Drug	Digoxin	Warfarin
Acarbose	Case reports[184-186] NS[187]	Case report[188]
Miglitol	+ 28%[69] a	NS[189]
Voglibose	NS[190,191]	NS[192]
Pioglitazone	NS[193]	NS [193]
Rosiglitazone	NS[194]	NA
Repaglinide	NS[178]	NS[195]
Nateglinide	NS[196]	NS[197] b

a Miglitol 100mg, three times daily

b Acenocoumarol instead of warfarin.

NA = no published data available; **NS** = no significant change.

rently.[214] Coadministration of these two drugs resulted in a mean 57% increase in steady-state plasma ciclosporin concentrations despite normal hepatic and renal functions. This elevation in ciclosporin concentration is possibly due to inhibition of CYP3A4-mediated metabolism of ciclosporin by glibenclamide. This observation calls for a closer monitoring of ciclosporin plasma concentrations during concomitant administration of these drugs.

No significant drug-drug interactions were observed when glibenclamide was used in combination with the calcium channel antagonist, nimodipine,[215] the non-opioid analgesic drug bromfenac[216] or thioctic acid (α-lipoic acid), a pharmacological agent used for the treatment of diabetic polyneuropathy.[217] In a pharmacokinetic interaction study, the plasma levels of both bosentan, a dual endothelin receptor antagonist, and glibenclamide were reduced after concomitant administration in healthy volunteers, a finding that is consistent with the CYP3A4-inducing potential of both drugs.[218] Finally, a two-period, randomised, double-blind, crossover, placebo-controlled study showed that eprosartan, an angiotensin II receptor antagonist, does not affect the pharmacodynamics of glibenclamide in patients with type 2 diabetes.[219]

Glipizide

In a randomised, placebo-controlled study, two groups of patients with type 2 diabetes who were stabilised on glipizide were given cimetidine (400mg) or ranitidine (150mg) 3 hours before a standardised meal.[220] In comparison with placebo, both cimetidine and ranitidine significantly reduced the postprandial blood glucose level by a mean of 40% and 25%, respectively ($p < 0.05$), producing glucose levels of <3 mmol/L in four patients. Both drugs also significantly increased the plasma glipizide AUC by approximately 20% ($p < 0.05$). It was concluded that caution should be exercised when treatment is initiated with H_2 receptor antagonists in type 2 diabetic patients receiving sulphonylureas.

In healthy volunteers, rifampicin decreased the AUC of glipizide by 22% ($p < 0.05$).[170] However, in contrast to what was observed in the same study with glibenclamide, no statistically significant differences in the blood glucose levels were found between the phases of glipizide administration with and without rifampicin. Induction of CYP2C9 by rifampicin would explain the increased systemic elimination of glipizide.

A published case report has indicated a possible pharmacokinetic interaction of glipizide with ciclosporin A in two diabetic patients who had undergone renal transplants.[221] However, an open prospective study showed that glipizide treatment does not interfere with ciclosporin pharmacokinetics in 11 diabetic renal allograft recipients.[222]

Gliclazide

Gliclazide is extensively metabolised, mainly by hydroxylation in the liver, and has no circulating active metabolite.[26] Gliclazide modified release employs a hydrophilic matrix that allows once-daily administration with 24-hour efficacy through the progressive delivery of short-acting gliclazide.[27] Furthermore, the modified release preparation demonstrates very high bioavailability, which allows reduction in the clinically effective gliclazide dose. Pharmacokinetics parameters are virtually unaffected by gastric pH, which reduces the risk of drug interactions with antacids or antisecretory agents.

An interaction between rifampicin and gliclazide has been reported as resulting in toxic hyperglycaemia in a patient with type 2 diabetes.[223] It was speculated that the induction of CYP2C9 by rifampicin might cause a decrease in the plasma concentrations of gliclazide. In a randomised, two-way crossover, placebo-controlled study in healthy Korean individuals, rifampicin decreased the mean AUC of glicazide plasma concentrations by 70% ($p < 0.001$) and the mean elimination half-life from 9.5 hours to 3.3 hours ($p < 0.05$).[171] The apparent oral clearance of gliclazide increased about 4-fold after rifampicin treatment ($p < 0.001$). A significant difference in the blood glucose response to gliclazide was observed between the placebo and rifampicin phases. Thus, the effects of rifampicin on the pharmacokinetics and pharmacodynamics of gliclazide suggest that rifampicin affects the disposition of gliclazide, possibly by the induction of CYP2C9. Concomitant use of rifampicin with gliclazide can reduce the glucose-lowering effect of gliclazide in patients with type 2 diabetes.

Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia has been reported in a HIV-infected patient.[224] It has been suggested that both fluconazole and sulfamethoxazole could inhibit CYP2C9 and lead to inhibition of gliclazide metabolism. Physicians should consider this potential interaction in the management of HIV-infected patients, in whom highly active antiretroviral therapy frequently triggers diabetes.[122]

Glimepiride

Glimepiride is a substrate of CYP2C9, and the importance of this metabolic pathway has been confirmed *in vivo* by comparing glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes.[201] Because rifampicin can induce CYP2C9-mediated drug metabolism, a study investigated the effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride in healthy volunteers.[172] Rifampicin decreased the mean AUC of glimepiride by 34% and the mean elimination half-life by 25%. Because the interaction was modest and did not significantly alter the glucose-lowering effect of glimepiride in healthy volunteers, it is probably of limited importance. However, in some diabetic patients the antihyperglycaemic effect of glimepiride may be reduced during concomitant treatment with rifampicin.

Fluconazole, an azole antimycotic known to be a potent inhibitor of CYP2C9, and some other CYP isoenzymes, considerably increased the AUC of plasma concentrations of glimepiride (+138%, $p < 0.001$) and prolonged its elimination half-life in healthy volunteers.[177] This was probably caused by inhibition of the CYP2C9-mediated transformation of glimepiride by fluconazole. Concomitant use of fluconazole with glimepiride in patients with type 2 diabetes may increase the risk of hypoglycaemia as much as would a 2- to 3-fold increase in the dose of glimepiride. In contrast, fluvoxamine, a selective serotonin reuptake inhibitor antidepressant that is a potent inhibitor of CYP1A2 and an inhibitor of several other CYP enzymes (including CYP2C9), only moderately increased the peak plasma concentrations of glimepiride and slightly prolonged the elimination half-life.[177]

Severe and persistent hypoglycaemia due to gatifloxacin interaction with glimepiride has been reported in one case report, an adverse effect that was also described with glibenclamide.[211]

In a recent German survey comparing the clinical characteristics and time course of severe hypoglycaemia whilst receiving glimepiride and the reference drug glibenclamide, no essential differences were observed between the two sulphonylurea compounds.[225] With regard to concomitant drugs that may potentially increase the risk of sulphonylurea-induced hypoglycaemia, 43% (40 of 93) of the diabetic patients were taking ACE inhibitors, 23% were taking β-blockers, 17% were taking sedatives or morphine and 6% were taking NSAIDs. Impaired renal function was present in 11 of the 13 patients with prolonged hypoglycaemia.

2.2.2 Metformin

The biguanides used for treatment of type 2 diabetes were introduced in the 1950s. Three drugs (metformin, phenformin and buformin) were initially marketed, but only metformin is still available since the withdrawal of phenformin and buformin because of an exaggerated risk of lactic acidosis, especially in diabetic patients with renal impairment. Several comprehensive reviews have been published on metformin, especially since this drug was introduced on the US market.[22-24,82,226]

Metformin is not metabolised in humans after oral or intravenous administration. No oxidative or conjugated metabolites of metformin have been observed in the plasma, urine or faeces. The drug is eliminated by renal excretion by way of active tubular secretion. Although many medications have been reported to interact with metformin, there are relatively few clinically important interactions.[24] This is largely because metformin is not protein bound and is not metabolised in the liver, making drug interactions through pharmacokinetic mechanisms rare.

In theory, because metformin is excreted predominantly through renal tubular secretion, medications that compete for this pathway or that have the ability to compromise renal function should not be coadministered with metformin, or dose reduction of metformin may need to be considered. Cationic drugs such as cimetidine, ranitidine, amiloride,

triamterene, quinine, quinidine, procainamide, digoxin, morphine, trimethoprim and vancomycin are all eliminated by the renal tubular route.[226] However, potential interactions with these cationic drugs eliminated by tubular secretion have not been observed in clinical practice.[227] Of these medications, the combination of metformin and cimetidine has been assessed in a well documented trial.[228] Cimetidine competes with metformin for a common transport system in the renal tubules reducing the rate of urinary excretion of metformin. The addition of cimetidine 400mg twice daily to metformin 250mg once daily in healthy volunteers produced a 50% increase in the plasma AUC of metformin and a 27% decrease in the 24-hour renal excretion of metformin. Thus, when it is not possible to avoid coadministration of drugs that may compete for renal tubular secretion or impair renal function, the patient should be monitored closely for signs and symptoms of toxicity and the dose of metformin should be modified accordingly.

In conclusion, there are almost no clinically relevant metabolic interactions with metformin, because it is not metabolised and does not inhibit the metabolism of other drugs.

2.2.3 α-Glucosidase Inhibitors

α-Glucosidase inhibitors competitively inhibit sucrase-isomaltase complexes.[66-70] As the inhibition of intestinal disaccharidases results in carbohydrates staying longer in the bowel, thus exerting osmotic activity and possibly altering the intestinal bacterial spectrum, it is possible that the absorption of other orally administered drugs might be affected. Potential interferences between α-glucosidase inhibitors and other glucose-lowering oral agents have already been discussed in sections 1.4, 1.5 and 1.6. Other potential drug-drug interactions have only been investigated between these agents and compounds with rather poor oral bioavailability and low therapeutic indices, such as digoxin and warfarin.

Acarbose

Acarbose was initially shown to decrease the absorption of coadministered digoxin.[184-186] However, more recent studies failed to show a significant interaction between digoxin and acarbose at current therapeutic doses (50mg three times daily) in healthy volunteers.[187] Nevertheless, the authors recognised that this interaction should be further studied with higher doses of acarbose and at steady-state conditions. If such an interaction exists, the precise mechanism of acarbose-induced reduction of digoxin levels remains unknown as voglibose, another α-glucosidase inhibitor, does not appear to share such an effect.

A probable interaction between acarbose and warfarin has been reported.[188] Since acarbose is not absorbed, this suspected interaction with warfarin is probably related to an increased absorption of warfarin. Further studies are needed to evaluate this potential interaction and determine its mechanism.

Miglitol

In healthy volunteers, concomitant use of miglitol 50mg or 100mg three times daily with digoxin reduced the average plasma concentrations of digoxin by 19% and 28%, respectively. However, in patients with type 2 diabetes, there were no effects on plasma digoxin concentrations with concomitant miglitol 300mg daily following 2-weeks' treatment.[69]

There were no significant effects of concomitant miglitol 100mg on the pharmacokinetics or pharmacodynamics of either (R)- or (S)-warfarin.[189] Similarly, miglitol did not alter the pharmacokinetics of phenytoin, an anticonvulsant whose bioavailability may be affected by changes in gastrointestinal functioning.[229] These investigations have involved short-term studies in healthy volunteers, so further studies in patients with type 2 diabetes may be required.

Concomitant administration of miglitol with propranolol or ranitidine reduced the absorption of these drugs, and thus the dose of these agents may require adjustment during concomitant use with miglitol.[69]

Voglibose

Voglibose (AO-128) is poorly absorbed from the gastrointestinal tract and hardly metabolised. Clinical trials revealed no detectable concentrations of the compound in either blood or urine samples. In contrast to acarbose, voglibose has been demonstrated to have no effect on the intestinal absorption of coadministered digoxin.[190,191] In a clinical trial performed in 12 healthy men, voglibose (5mg three times daily) modified neither the pharmacodynam-

ics nor the pharmacokinetics of warfarin under steady-state conditions.[192]

2.2.4 Thiazolidinediones

The first drug in this class to be approved in the US was troglitazone in 1997. However, it was associated with an elevation of serum alanine aminotransferase (ALT) levels in approximately 1–2% of patients and, in rare cases, hepatic failure and death.[48] It was, therefore, withdrawn from the market in 2000. Subsequent to the launch and withdrawal of troglitazone, two other thiazolidinediones entered the market, pioglitazone and rosiglitazone. The major question about the use of new PPAR-γ agonists in general, and the thiazolidinediones in particular, is whether the liver toxicity observed with troglitazone is unique to troglitazone or represents a class effect. Pioglitazone and rosiglitazone appear to be safe, although limited, poorly documented, cases of liver toxicity have also been reported.[48,230] It is noteworthy that abnormal liver function tests are common in the overweight/obese population, especially in patients with type 2 diabetes.[231] However, the prevalence of elevated ALT levels is not higher with second-generation thiazolidinediones than with other oral antidiabetic agents.[232] In contrast, both pioglitazone[233] and rosiglitazone[234] have been shown to reduce elevated ALT levels compared with placebo or other oral antihyperglycaemic compounds in phase III trials. Another concern about the use of thiazolidinediones is oedema and heart failure, especially in diabetic patients treated with insulin.[235] Although the precise mechanism of such adverse effects remains poorly understood, one possible explanation is that thiazolidinediones may potentiate the effects of insulin on renal sodium and water retention.

Troglitazone has been associated with significant clinical drug interactions due to liver enzyme induction, particularly when used with compounds that are substrates for CYP3A4.[236] For instance, a potential interaction exists between troglitazone and ciclosporin A, as seven transplant recipients who had been started on troglitazone therapy experienced a statistically and clinically significant decrease in ciclosporin A trough levels immediately after the institution of troglitazone therapy.[237] An *in vitro* study showed that all three thiazolidinediones (troglitazone, pioglitazone and rosiglitazone) have the potential to induce CYP3A4.[133] The *in vitro* inhibition data indicate that, in general, troglitazone is the most potent CYP inhibitor of the three compounds. As already mentioned, there are no reports on the clinical induction of CYP enzymes by rosiglitazone or pioglitazone to date. The apparent absence of clinical effects of CYP enzyme inhibition may be due to either a lack of clinical data (CYP2C8), overwhelming CYP induction (CYP3A4) or reasons we do not yet understand (CYP2C9). It is the last of these scenarios that requires additional research in order to better use *in vitro* inhibition data to predict potential drug-drug interactions of these and future thiazolidinediones.[133]

Pioglitazone

Pioglitazone undergoes extensive hepatic metabolism, predominantly via the CYP2C8 system. Secondary pathways include CYP3A4, CYP2C9 and CYP1A1/2.[49] Although pioglitazone is partially metabolised via CYP3A4,[49] no evidence exists *in vivo* that pioglitazone induces hepatic CYP3A4 activity.[238]

Pioglitazone seems to have only a small potential for drug interactions in patients with type 2 diabetes. It has been reported to slightly reduce the plasma concentrations of midazolam or nifedipine (by 10–30%). Single and repeated dosages of pioglitazone 45mg daily were coadministered with warfarin, phenprocoumon, glipizide, metformin or digoxin in healthy volunteers.[193] The data suggest pioglitazone does not affect the pharmacokinetics and pharmacodynamics of any of these drugs and does not appear to induce or inhibit the CYP isoenzyme system.[49]

Lack of induction or inhibition of hepatic enzyme systems was also indicated by data that showed no statistically or clinically significant effect of pioglitazone 45mg daily on the pharmacokinetics of ethinylestradiol/norethindrone or ethinylestradiol/estrone as used in oral contraceptive or hormone replacement therapy regimens.[239]

Rosiglitazone

CYP2C8 is primarily responsible for the hydroxylation and N-demethylation of rosiglitazone in human liver, with minor contributions from

CYP2C9.[240] Therefore, rosiglitazone pharmacokinetics may be affected by CYP2C9 inducers, such as rifampicin, or by CYP2C9 inhibitors, such as gemfibrozil or trimethoprim.

In a randomised, open-label, two-way crossover study in Korean men, rifampicin significantly decreased the mean AUC of rosiglitazone concentrations by 65% and the mean elimination half-life from 3.9 hours to 1.5 hours.[175] The apparent oral clearance of rosiglitazone increased about 3-fold after rifampicin treatment ($p < 0.001$). These observations were confirmed in a Finnish randomised, crossover trial in healthy volunteers.[176] Rifampicin reduced the AUC and C_{max} of rosiglitazone by 54% and 28%, respectively; the elimination half-life of rosiglitazone was shortened from 3.8 hours to 1.9 hours. Rifampicin increased the formation of N-desmethylrosiglitazone by about 40% ($p < 0.0001$). Thus, rifampicin affected the disposition of rosiglitazone in humans, probably by the induction of CYP2C8 and, to a lesser extent, CYP2C9. Therefore, caution should be exercised during coadministration of rifampicin and rosiglitazone in clinical practice.

In healthy volunteers, trimethoprim, a relatively selective inhibitor of CYP2C8, raised the AUC of plasma rosiglitazone concentrations by 37% and the C_{max} by 14%.[176] The elimination half-life of rosiglitazone was prolonged from 3.8 hours to 4.8 hours ($p = 0.0003$). Trimethoprim reduced the formation of N-desmethylrosiglitazone by 36%. As previously emphasised, gemfibrozil, another CYP2C8 inhibitor, almost doubled both the mean plasma AUC and the elimination half-life of rosiglitazone in healthy volunteers.[151] Therefore, coadministration of gemfibrozil and rosiglitazone should be considered with caution in diabetic patients and the dose of rosiglitazone adjusted accordingly to reduce the risk of adverse effects.

The effect of sucralfate (an antiulcer agent) pretreatment on the single-dose pharmacokinetics of oral rosiglitazone 8mg was investigated in healthy volunteers.[241] No statistically significant differences were observed for any of the calculated rosiglitazone pharmacokinetic parameters in participants who did or did not receive pretreatment with sucralfate. Similarly, in another study in 12 healthy male volunteers, the pharmacokinetic parameters after oral (4mg) and intravenous (2mg) single doses of rosiglitazone were unaltered by concurrent treatment with ranitidine.[183] This absence of rosiglitazone interference with H_2 receptor antagonists contrasts with previous reports that showed a potential interference of cimetidine and ranitidine with sulphonylurea compounds such as glibenclamide and glipizide.[212,213,220]

Rosiglitazone does not markedly alter CYP3A4-mediated drug metabolism.[242] Rosiglitazone is primarily metabolised by CYP2C8 and has shown no clinically significant interactions with CYP3A4-metabolised substrates such as nifedipine[243] and oral contraceptives.[244]

The interaction of rosiglitazone with oral digoxin was investigated in healthy volunteers.[194] Coadministration of digoxin 0.375mg with rosiglitazone 8mg had no significant effect on the safety or steady-state pharmacokinetics of digoxin.

2.2.5 Meglitinide Derivatives

The potential of drug-drug interaction with the new insulin secretagogues repaglinide and nateglinide has been extensively studied during recent years, as these two drugs are metabolised through the CYP system and have been presented as being safer for use in clinical practice than sulphonylureas.

Repaglinide

Repaglinide is rapidly absorbed and has a plasma half-life of approximately 1 hour.[245] It is highly bound (98%) to plasma proteins. However, *in vitro* experimental data indicate a low potential for protein binding drug interactions associated with repaglinide.[246] Repaglinide is extensively metabolised by direct glucuronidation and oxidation. The metabolites are not pharmacologically active. An important role for both CYP3A4 and CYP2C8 in the transformation of repaglinide has been reported in studies of human liver microsomes.[247] The contribution of CYP2C8 to the metabolism of repaglinide was further demonstrated *in vivo* by showing that polymorphism in CYP2C8 was associated with reduced plasma concentrations of repaglinide.[248] This dual CYP biotransformation may have consequences for the clinical pharmacokinetics and drug-drug interactions of repaglinide if one CYP pathway has sufficient capacity to compensate if the other is inhibited. Indeed, metabolism by both these enzymes may

explain why selective inhibition and possibly induction of CYP3A4 in humans has a less than expected effect on the pharmacokinetics and hypoglycaemic action of repaglinide.[133,247]

As one of the principal CYP isoforms involved in repaglinide metabolism in human liver microsomes is CYP3A4, inhibitors of CYP3A4 activity (e.g. antifungal agents such as ketoconazole) or inducers of CYP3A4 activity (e.g. rifampicin) may thus influence the pharmacokinetics of repaglinide.[133] In two randomised, two-period, open-label, crossover studies healthy individuals received repaglinide alone, repaglinide on day 7 of rifampicin treatment or repaglinide on day 5 of ketoconazole treatment.[133] Concomitant rifampicin decreased the mean AUC for repaglinide by 31% and the mean C_{max} by 26%. Compared with the administration of repaglinide alone, concomitant ketoconazole increased the mean AUC for repaglinide by 15% and the mean C_{max} by 7%. Thus, the pharmacokinetic profile of repaglinide was altered by the administration of potent CYP3A4 inducers or inhibitors such as rifampicin or ketoconazole, but to a lesser degree than expected. Profiles of blood glucose levels following repaglinide administration were altered by <8% by both rifampicin and ketoconazole. The safety profile of repaglinide was not altered by pre-treatment with rifampicin or ketoconazole. In another study, rifampicin 600mg once daily for 5 days decreased plasma concentrations of repaglinide after a single 0.5mg dosage on day 6 (AUC −57%, $p < 0.001$) and correspondingly reduced the blood glucose lowering effect of repaglinide.[173] In contrast, the CYP3A4 inhibitor clarithromycin increased the plasma concentrations of repaglinide (C_{max} +67%; AUC +40%).[180] Consequently, plasma insulin levels were significantly increased when repaglinide was combined with clarithromycin compared with placebo. However, no statistically significant differences were found in blood glucose concentrations between the two experimental phases. Similarly, the CYP2C8 inhibitor trimethoprim increased the plasma concentrations (C_{max} +41%; AUC +61%) of repaglinide in healthy individuals.[179] Although the interaction did not significantly enhance the effect of repaglinide on blood glucose level at the drug doses used, the possibility of an increased risk of hypoglycaemia should be considered during concomitant use of clarithromycin or trimethoprim and repaglinide in patients with diabetes. Finally, as already pointed out, the AUC of repaglinide showed a 8-fold increase when coadministered with gemfibrozil alone (a CYP2C8 inhibitor), a 1.4-fold increase in combination with itraconazole alone (a CYP3A4 inhibitor) and a 20-fold increase when administered with the gemfibrozil-itraconazole combination.[148] Thus, gemfibrozil considerably enhanced and prolonged the blood glucose-lowering effect of repaglinide, i.e. repaglinide became a long-acting and stronger antidiabetic agent. Unlike gemfibrozil, bezafibrate and fenofibrate have no significant effects on the pharmacokinetics and pharmacodynamics of repaglinide, and thus, can be safely used in combination with repaglinide in diabetic patients who should be prescribed fibric acid derivatives for the treatment of dyslipidaemia.[149] Consequently, careful monitoring of blood glucose levels in repaglinide-treated diabetic patients receiving strong inducers or inhibitors of CYP3A4 or CYP2C8 is recommended and a change in repaglinide dose may be necessary in such circumstances.

Despite its effect on the gastric pH and inhibition of the hepatic CYP system, cimetidine 400mg twice daily had no effect on the mean serum profile of repaglinide or on any of the mean pharmacokinetic parameters of a single 2mg dose of repaglinide, administered following multiple doses of cimetidine.[178] Similarly, coadministration of cimetidine (800mg daily for 5 days) with repaglinide (2mg three times daily for 4 days) did not change repaglinide pharmacokinetics from control values, or result in hypoglycaemia.[249] Based on these results, no dose adjustments appear to be necessary for repaglinide or cimetidine during coadministration of these drugs.

In three randomised, three-period, open-label crossover studies in healthy individuals, no clinically relevant pharmacokinetic interactions occurred between repaglinide and the CYP3A4 substrates ethinylestradiol/levonorgestrel, simvastatin and nifedipine.[132] However, the incidence of adverse events increased with coadministration of simvastatin or nifedipine and repaglinide compared with either repaglinide, simvastatin or nifedipine treatment alone.

Drug interaction studies for repaglinide and digoxin, theophylline and warfarin,[178,195,250] three commonly prescribed medications that may give rise to adverse effects because of a narrow therapeutic margin, have been performed in healthy individuals. The studies demonstrated no risk of significant interactions. The pharmacokinetics of digoxin, administered as a loading dosage of 0.5mg followed by 0.25 mg/day for 9 days, was unaffected by coadministration of repaglinide 2mg three times daily.[178] Mean theophylline AUC values were equivalent during monotherapy (300mg taken orally, twice daily) and coadministration with repaglinide (2mg three times daily).[178] Repaglinide 2mg taken three times daily had no clinically relevant effects on the pharmacokinetics of warfarin (individually dose-titrated, with both drugs at steady state) and no effect on prothrombin measurements.[195]

Thus, in clinical practice, a dose increase may be indicated to obtain optimal glucose control when repaglinide is coadministered with potent inducers of CYP3A4, such as rifampicin or carbamazepine, whereas a dose decrease may be indicated when repaglinide is coadministered with potent inhibitors of CYP3A4, such as ketoconazole or clarithromycin, in order to avoid hypoglycaemia.[251]

Nateglinide

According to *in vitro* data obtained using human liver microsomes, CYP enzymes CYP2C9, CYP2D6 and CYP3A4 appear to mediate nateglinide biotransformation reactions and CYP2C9 appears to be the predominant enzyme (responsible for about 70% of nateglinide intrinsic clearance).[97,251] A prospective clinical study in healthy volunteers chosen for their CYP2C9 and CYP2D6 genotypes was conducted, with individuals carrying wild-type genotypes as the reference group.[252] Significantly reduced oral nateglinide clearance was found in carriers of *CYP2C9**3* alleles, without statistically significant differences in plasma glucose, insulin and glucagon levels. Nevertheless, it was concluded that the effect of CYP2C9 polymorphisms on nateglinide kinetics may cause a slightly increased risk of hypoglycaemia in diabetic patients. Consequently, drug interactions with substrates of CYP3A4 and CYP2C9 might be anticipated for nateglinide.[97]

In a two-phase, randomised, crossover study, 10 healthy volunteers took 600mg rifampicin or placebo orally once daily for 5 days, and ingested a single 60mg dose of nateglinide on day 6 of both phases.[174] Rifampicin decreased the mean AUC of nateglinide by 24%, but had no significant effect on the blood glucose-lowering effect of nateglinide. Thus rifampicin, a potent inducer of several drug-metabolising enzymes (including CYP2C9 and CYP3A4) and of some drug transporters, only modestly decreased the plasma concentrations of nateglinide, probably by inducing its oxidative biotransformation. However, in some patients, rifampicin may reduce the blood-glucose lowering effect of nateglinide.

Fluconazole (400mg on day 1 and 200mg on days 2–4), an inhibitor of CYP2C9, CYP2C19 and CYP3A4, increased the AUC of nateglinide by 48% ($p < 0.00001$) and impaired the formation of the M7 metabolite of nateglinide (a dehydro derivative).[181] Despite the fact that no significant differences were seen in the blood glucose response to nateglinide between fluconazole and placebo phases in this study performed in healthy volunteers, one cannot exclude the possibility that concomitant use of fluconazole and nateglinide may prolong the blood glucose-lowering effect of nateglinide in patients with type 2 diabetes.

The effect of a potent and selective CYP2C9 inhibitor, sulfinpyrazone, on the pharmacokinetics of nateglinide was evaluated in healthy individuals.[182] Sulfinpyrazone increased the mean exposure to nateglinide by 28% ($p < 0.01$) when these drugs were administered in combination, with no differences in the C_{max}, t_{max} and elimination half-life of nateglinide.

In vitro, nateglinide has been found to inhibit the metabolism of tolbutamide (a CYP2C9 substrate), but no inhibition of CYP3A4 metabolic reactions has been detected. Drug-drug interaction studies in healthy individuals have shown no interaction between nateglinide and a single dose of diclofenac 75mg (a substrate of CYP2C9)[253] or a single dose of warfarin 30mg (a substrate for CYP3A4 and CYP2C9),[254] when nateglinide was administered at a dose of 120mg before meals. Similarly, coadministration of nateglinide did not influence either the pharmacokinetics or the anticoagulant activity of

(R)- and (S)-acenocoumarol in healthy individuals.[197] This absence of drug-drug interaction is observed despite the fact that the two drugs are primarily metabolised via CYP2C9. This suggests that no dose adjustments will be required when nateglinide and acenocoumarol are coadministered in clinical practice. Based on the results obtained with these substrates, the potential for nateglinide to inhibit the metabolism of other drugs is small. Similarly, the potential for other drugs to increase nateglinide concentrations is limited, although clinical studies with a CYP2C9 inhibitor would be required to fully explore the primary metabolic pathway of nateglinide.[97]

No drug interaction was reported between nateglinide and a single dose of digoxin 1mg in a study in which nateglinide 120mg was given three times daily before meals to healthy subjects for 2 days.[196] In this partially randomised, nonblind, crossover study, the concurrent administration of nateglinide and digoxin did not affect the pharmacokinetics of either drug, nor was there evidence of pharmacodynamic interactions, assessed on the basis of cardiac and haemodynamic assessments.

Finally, as nateglinide is highly bound to plasma proteins, this may be a potential site of drug-drug interactions. However, *in vitro* displacement studies have shown no influence of highly protein-bound drugs on the pharmacokinetics of nateglinide and conversely no influence by nateglinide has been detected on the protein binding of various drugs.[97]

3. Conclusion

Now that it is recognised that the glucose-lowering effects of the different classes of antidiabetic agents are additive while their adverse effects are usually not, combination therapy has become widely accepted for the management of type 2 diabetes. Beside the classic sulphonylurea-metformin combination, new combined therapies are now available, especially metformin plus thiazolidinedione or sulphonylurea plus thiazolidinedione. Meglitinide derivatives may be considered as an alternative to sulphonylureas to better control postprandial hyperglycaemia and/or to reduce the risk of hypoglycaemia. Finally, α-glucosidase inhibitors are generally used as add-on therapy to improve overall metabolic control and dampen the variability of blood glucose. The increasing complexity of diabetes care may expose the diabetic patient to a higher risk of drug interactions. However, no deleterious drug-drug interactions have been described when oral antihyperglycaemic agents are coadministered. The only problem may consist of a higher rate of hypoglycaemic episodes, which may require appropriate dose adjustment of glucose-lowering agents, especially insulin secretagogues (sulphonylureas and meglitinide derivatives). As prevention of cardiovascular complications is becoming a major objective in patients with type 2 diabetes, coadministration of lipid-lowering drugs or antihypertensive agents is common. Drug-drug interactions between oral antidiabetic agents and statins or fibric acid derivatives are *usually* of minor clinical importance. However, a major pharmacokinetic interaction of gemfibrozil with repaglinide, and to a lesser extent, with rosiglitazone, has been described and coprescription of these drugs should be avoided or deserves caution.

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References

1. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003; 46: 3-19
2. Scheen AJ. Pathophysiology of type 2 diabetes. Acta Clin Belg 2003; 58: 335-41
3. Scheen AJ, Lefbèvre PJ. Oral antidiabetic agents: a guide to selection. Drugs 1998; 55: 225-36
4. Lebovitz HE. Oral therapies for diabetic hyperglycemia. Endocrinol Metab Clin N Am 2001; 30: 909-33
5. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002; 287: 360-72
6. Charpentier G. Oral combination therapy for type 2 diabetes. Diabetes Metab Res Rev 2002; 18 Suppl. 3: S70-6
7. Van Gaal LF, De Leeuw I. Rationale and options for combination therapy in the treatment of type 2 diabetes. Diabetologia 2003; 46 Suppl. 1: M44-50
8. Scheen AJ. Current management of coexisting obesity and type 2 diabetes. Drugs 2003; 63: 1165-84
9. Hu G, Qiao Q, Tuomilehto J, et al. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. DECODE Study Group. Arch Intern Med 2004; 164: 1066-76
10. Grundy SM, Hansen B, Smith SC, et al. Clinical management of metabolic syndrome. Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association: conference on scientific issues related to management. Circulation 2004; 109: 551-6

11. Scheen AJ. Management of the metabolic syndrome. Minerva Endocrinol 2004; 29: 31-45
12. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383-93
13. Gale E. The polypill and type 2 diabetes. Diabet Med 2004; 21: 8-10
14. Grant RW, Pirraglia PA, Meigs JB, et al. Trends in complexity of diabetes care in the United States from 1991 to 2000. Arch Intern Med 2004; 164: 1134-9
15. Scheen AJ, Lefèbvre PJ. Antihyperglycaemic agents: drug interactions of clinical importance. Drug Saf 1995; 12: 32-45
16. Scheen AJ. Drug treatment of non-insulin-dependent diabetes mellitus in the 1990s: achievements and future developments. Drugs 1997; 54: 355-68
17. Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Saf 1994; 11: 223-41
18. Davidson MB. Triple therapy: definitions, application, and treating to target. Diabetes Care 2004; 27: 1834-5
19. Ahmann AJ, Riddle MC. What to do when two oral agents fail to control type 2 diabetes: a matter of opinion or a matter of fact? Am J Med 2004; 116: 276-8
20. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. Drugs 2004; 64: 1339-58
21. Riddle M. Combining sulfonylureas and other oral agents. Am J Med 2000; 108 Suppl 6a: 15S-22S
22. Dunn CJ, Peters DH. Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. Drugs 1995; 49: 721-49
23. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. Diabetes Rev 1998; 6: 89-131
24. Setter SM, Iltz JL, Thams J, et al. Metformin hydrochloride in the treatment of type 2 diabetes mellitus: a clinical review with a focus on dual therapy. Clin Ther 2003; 25: 2991-3027
25. Hermann LS, Schersten B, Bitzen PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: a double-blind controlled study. Diabetes Care 1994; 17: 1100-9
26. Palmer KJ, Brodgen RN. Gliclazide, an update on its pharmacological properties and therapeutic efficacy in non-insulin-dependent diabetes mellitus. Drugs 1993; 46: 92-125
27. Mc Gavin JK, Perry CM, Goa KL. Gliclazide modified release. Drugs 2002; 62: 1357-64
28. Langtry HD, Balfour JA. Glimepiride: a review of its use in the management of type 2 diabetes mellitus. Drugs 1998; 55: 563-84
29. McCall AL. Clinical review of glimepiride. Expert Opin Pharmacother 2001; 2: 699-713
30. Massi-Nenedetti M. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. Clin Ther 2003; 25: 799-816
31. Charpentier G, Fleury F, Kabir M, et al. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med 2001; 18: 828-34
32. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004; 34: 535-42
33. Marathe PH, Arnold ME, Meeker J, et al. Pharmacokinetics and bioavailability of a metformin/glyburide tablet administered alone and with food. J Clin Pharmacol 2000; 40: 1494-502
34. Blonde L, Rosenstock J, Mooradian AD, et al. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulfonylurea therapy. Diabetes Obes Metab 2002; 4: 368-75
35. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glibenclamide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab 2002; 4: 201-8
36. Marre M, Howlett H, Lehert P, et al. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance®) in type 2 diabetic patients inadequately controlled with metformin. Diabet Med 2002; 19: 673-80
37. Garber AJ, Bruce S, Fiedorek FT. Durability of efficacy and long-term safety profile of glyburide/metformin tablets in patients with type 2 diabetes mellitus: an open-label extension study. Clin Ther 2002; 24: 1401-13
38. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomised, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. Clin Ther 2003; 25: 890-903
39. UKPDS Prospective Diabetes Study Group. Effects of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65
40. Mooradian AD, Chehade J. Implications of the UK Prospective Diabetes Study: questions answered and issues remaining. Drugs Aging 2000; 16: 159-64
41. Olsson J, Lindberg G, Gottsater M, et al. Increased mortality in type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. Diabetologia 2000; 43: 558-60
42. Fisman EZ, Tenenbaum A, Boyko V, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol 2001; 24: 151-8
43. Mannucci E, Monami M, Masotti G, et al. All-cause mortality in diabetic patients treated with combinations of sulfonylureas and biguanides. Diabetes Metab Res Rev 2004; 20: 44-7
44. Braunstein S. New developments in type 2 diabetes mellitus: combination therapy with a thiazolidinedione. Clin Ther 2003; 25: 1895-917
45. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. Drugs 2003; 63: 1373-405
46. Meriden T. Progress with thiazolidinediones in the management of type 2 diabetes mellitus. Clin Ther 2004; 26: 177-90
47. Martens FMAC, Visseren FLJ, Lemay J, et al. Metabolic and additional vascular effects of thiazolidinediones. Drugs 2002; 62: 1463-80
48. Scheen AJ. Hepatotoxicity with thiazolidinediones: is it a class effect? Drug Saf 2001; 24: 873-88
49. Gillies PS, Dunn CJ. Pioglitazone. Drugs 2000; 60: 333-43
50. Chilcott J, Tappenden P, Jones ML, et al. A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. Clin Ther 2001; 23: 1792-823
51. Balfour JA, Plosker GL. Rosiglitazone. Drugs 1999; 57: 921-30
52. Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. Drugs 2002; 62: 1805-37
53. Kaneko T, Baba S, Toyota T. Dose finding study of AD-4833 in patients with NIDDM on treatment with a sulphonylurea drug: single blind comparative study of four dosages. Jpn J Clin Exp Med 1997; 74: 1278-306
54. Kaneko T, Baba S, Toyota T. Clinical evaluation of an insulin-resistance improving agent, AD-4833, in patients with NIDDM on treatment with SU drug: a placebo controlled double blind clinical study. Jpn J Clin Exp Med 1997; 74: 1515-39
55. Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomised, placebo-controlled study. Am J Med 2001; 111: 10-7

56. Wolffenbuttel BH, Gomis R, Squatrito S, et al. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients. Diabet Med 2000; 17: 40-7
57. Vongtharavat V, Wajchenberg BL, Waitman JN, et al. An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes: 125 Study Group. Curr Med Res Opin 2002; 18: 456-61
58. Derosa G, Cicero AFG, Gaddi A, et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. Clin Ther 2004; 26: 744-54
59. Inzucchi SE, Maggs DG, Spollett GR, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 1998; 338: 867-72
60. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomised, placebo-controlled study. The Pioglitazone 027 Study Group. Clin Ther 2000; 22: 1395-409
61. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomised controlled trial. JAMA 2000; 283: 1695-702
62. Gomez-Perez FJ, Fanghanel-Salmon G, Barbosa AJ, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. Diabetes Metab Res Rev 2002; 18: 127-34
63. Rendell M, Glazer NB, Ye Z. Combination therapy with pioglitazone plus metformin or sulfonylurea in patients with type 2 diabetes: influence of prior antidiabetic drug regimen. J Diabet Complications 2003; 17: 211-7
64. Hanefeld M, Brunetti P, Schernathaner GH, et al. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. Diabetes Care 2004; 27: 141-7
65. Di Cicco RA, Allen A, Carr A, et al. Rosiglitazone does not alter the pharmacokinetics of metformin. J Clin Pharmacol 2000; 40: 1280-5
66. Clissold SP, Edwards C. Acarbose: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1988; 35: 214-43
67. Balfour JA, McTavish D. Acarbose: an update of its pharmacology and therapeutic use in diabetes mellitus. Drugs 1993; 46: 1025-54
68. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. Clin Pharmacokinet 1996; 30: 94-106
69. Scott LJ, Spencer CM. Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus. Drugs 2000; 59: 521-49
70. Göke B, Fuder H, Wieckhorst G, et al. Voglibose (AO-128) is an efficient α-glucosidase inhibitor and mobilizes the endogenous GLP-1 reserve. Digestion 1995; 56: 493-501
71. Scheen AJ. Clinical efficacy of acarbose in the treatment of diabetes: a critical review of controlled trials. Diabetes Metab 1998; 24: 311-20
72. Breuer HW. Review of acarbose therapeutic strategies in the long-term treatment and in the prevention of type 2 diabetes. Int J Clin Pharmacol Ther 2003; 41: 421-40
73. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). Diabetes Care 1999; 22: 960-4
74. Costa B, Pinol C. Acarbose in ambulatory treatment of non-insulin-dependent diabetes mellitus associated to imminent sulfonylurea failure: a randomised-multicentric trial in primary health care. Diabetes and Acarbose Research Group. Diabetes Res Clin Pract 1997; 38: 33-40
75. Willms B, Ruge D. Comparison of acarbose and metformin in patients with type 2 diabetes mellitus insufficiently controlled with diet and sulphonylureas: a randomised, placebo-controlled study. Diabet Med 1999; 16: 755-61
76. Johnston PS, Coniff RF, Hoogwerf BJ, et al. Effects of the carbohydrase inhibitor miglitol in sulfonylurea-treated NIDDM patients. Diabetes Care 1994; 17: 20-9
77. Johnston PS, Feig PU, Coniff RF, et al. Chronic treatment of African-American type 2 diabetic patients with α-glucosidase inhibition. Diabetes Care 1998; 21: 416-22
78. Matsumoto K, Sera Y, Abe Y, et al. Combination therapy of alpha-glucosidase inhibitor and a sulfonylurea compound prolongs the duration of good glycemic control. Metabolism 2002; 51: 1548-52
79. Gérard J, Lefèbvre PJ, Luyckx AS. Glibenclamide pharmacokinetics in acarbose-treated type 2 diabetics. Eur J Clin Pharmacol 1984; 27: 233-6
80. Scheen AJ, Lefèbvre PJ. Potential pharmacokinetics interferences between α-glucosidase inhibitors and other antidiabetic agents [letter]. Diabetes Care 2002; 25: 247-8
81. Kleist P, Ehrlich A, Suzuki Y, et al. Concomitant administration of the α-glucosidase inhibitor voglibose (AO-128) does not alter the pharmacokinetics of glibenclamide. Eur J Clin Pharmacol 1997; 53: 149-52
82. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 1996; 30: 359-71
83. Scheen AJ, Ferreira Alves de Magalhaes C, Salvatore T, et al. Reduction of the acute bioavailability of metformin by the α-glucosidase inhibitor acarbose in normal man. Eur J Clin Invest 1994; 24 Suppl. 3: 50-4
84. Rosenstock J, Brown A, Fischer J, et al. Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. Diabetes Care 1998; 21: 2050-5
85. Halimi S, Le Berre MA, Grange V. Efficacy and safety of acarbose add-on therapy in the treatment of overweight patients with type 2 diabetes inadequately controlled with metformin: a double-blind, placebo-controlled study. Diabetes Res Clin Pract 2000; 50: 49-56
86. Phillips P, Karrasch J, Scott R, et al. Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. Diabetes Care 2003; 26: 269-73
87. Chiasson J-L, Naditch L. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes: Miglitol Canadian University Investigator Group. Diabetes Care 2001; 24: 989-94
88. Bando Y, Ushiogi Y, Okafuji K, et al. Troglitazone combination therapy in obese type 2 diabetic patients poorly controlled with alpha-glucosidase inhibitors. J Int Med Res 1999; 27: 53-64
89. Miller AK, Inglis AM, Thompson Culkin K, et al. The effect of acarbose on the pharmacokinetics of rosiglitazone. Eur J Clin Pharmacol 2001; 57: 105-9
90. Hayashi Y, Miyachi N, Takeuchi T, et al. Clinical evaluation of pioglitazone in patients with type 2 diabetes using α-glucosidase inhibitor and examination of its efficacy profile. Diabetes Obes Metab 2003; 5: 58-65
91. Seino H, Yamaguchi H, Misaki A, et al. Clinical effect of combination therapy of pioglitazone and an alpha-glucosidase inhibitor. Curr Med Res Opin 2003; 19: 675-82
92. Dornhorst A. Insulinotropic meglitinide analogues. Lancet 2001; 358: 1709-16
93. Owens DR. Repaglinide: prandial glucose regulator: a new class of oral antidiabetic drug. Diabet Med 1998; 15 Suppl. 4: S28-36
94. Cully CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. Drugs 2001; 61: 1625-60

95. Dunn CJ, Faulds D. Nateglinide. Drugs 2000; 60: 607-15
96. Norman P, Rabasseda X. Nateglinide: a structurally novel insulin secretion agent. Drugs Today (Barc) 2001; 37 Suppl. F: 1-16
97. McLeod JF. Clinical pharmacokinetics of nateglinide: a rapidly-absorbed, short-acting insulinotropic agent. Clin Pharmacokinet 2004; 43: 97-120
98. Moses R. Repaglinide in combination therapy. Diabetes Nutr Metab 2002; 15 (6 Suppl.): 33-8
99. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 1999; 22: 119-24
100. Hirshberg Y, Karara AH, Pietri AO, et al. Improved control of mealtime glucose excursions with coadministration of nateglinide and metformin. Diabetes Care 2000; 23: 349-53
101. Horton ES, Clinkingbeard C, Galtin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care 2000; 23: 1660-5
102. Marre M, Van Gaal L, Usadel KH, et al. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes Obes Metab 2002; 4: 177-86
103. Salas M, Ward A, Caro J. Health and economic effects of adding nateglinide to metformin to achieve dual control of glycosylated hemogobin and postprandial glucose levels in a model of type 2 diabetes mellitus. Clin Ther 2002; 24: 1690-705
104. Raskin P, Klaff L, McGill S, et al. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. Diabetes Care 2003; 26: 2063-8
105. Raskin P, Jovanovic L, Berger S, et al. Repaglinide-troglitazone combination therapy: improved glycemic control in type 2 diabetes. Diabetes Care 2000; 23: 979-83
106. Rosenstock J, Shen SG, Gatlin MR, et al. Combination therapy with nateglinide and a thiazolidinedione improves glycemic control in type 2 diabetes. Diabetes Care 2002; 25: 1529-33
107. Jovanovic L, Hassman DR, Gooch B, et al. Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone: Repaglinide/Pioglitazone Study Group. Diabetes Res Clin Pract 2004; 63: 127-34
108. Gavin LA, Barth J, Arnold D, et al. Troglitazone add-on therapy to a combination of sulphonylureas plus metformin achieved and sustained effective diabetes control. Endocr Pract 2000; 6: 305-10
109. Yale J, Valiquett T, Ghazzi M, et al. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes poorly controlled with sulphonylurea and metformin: a multicenter, randomized, double-blind, placebo-controlled trial. Troglitazone Triple-Therapy Study Group. Ann Intern Med 2001; 134: 737-45
110. Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004; 116: 230-5
111. Kiayias JA, Vlachou ED, Theodosopoulou E, et al. Rosiglitazone in combination with glimepiride plus metformin in type 2 diabetic patients. Diabetes Care 2002; 25: 1251-2
112. Bell DSH, Ovalle F. Long-term efficacy of triple oral therapy for type 2 diabetes mellitus. Endocr Pract 2002; 8: 271-5
113. Roy R, Navar M, Palomeno G, et al. Real world effectiveness of rosiglitazone added to maximal (tolerated) doses of metformin and a sulfonylurea agent: a systematic evaluation of triple oral therapy in a minority population. Diabetes Care 2004; 27: 1741-2
114. Dailey GE, Noor MA, Park J-S, et al. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med 2004; 116: 223-9
115. Schwartz S, Sievers R, Strange P, et al. Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost-analysis. Diabetes Care 2003; 26: 2238-43
116. Brian WR. Hypoglycemic agents. In: Levy RH, Thummel KE, Trager WF, et al, editors. Metabolic drug interactions. Philadelphia (PA): Lippincott Williams & Wilkins, 2000: 529-43
117. Marks V, Teale JD. Drug-induced hypoglycemia. Endocrinol Metab Clin North Am 1999; 28: 555-77
118. Holstein A, Egberts EH. Risk of hypoglycaemia with oral antidiabetic agents in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2003; 111: 405-14
119. Collin M, Mucklow JC. Drug interactions, renal impairment and hypoglycaemia in a patient with type II diabetes. Br J Clin Pharmacol 1999; 48: 134-7
120. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clin Pharmacokinet 2002; 41: 343-70
121. Shorr RI, Ray WA, Daugherty JR, et al. Antihypertensives and the risk of serious hypoglycemia in old persons using insulin or sulfonylureas. JAMA 1997; 278: 40-3
122. Fichtenbaum CJ, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. Clin Pharmacokinet 2002; 41: 1195-211
123. Melkersson K, Dahl M-L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs 2004; 64: 701-23
124. DeVane CL, Markowitz JS. Psychoactive drug interactions with pharmacotherapy for diabetes. Psychopharmacol Bull 2002; 36: 40-52
125. Haffner SM. Statin therapy for the treatment of diabetic dyslipidemia. Diabetes Metab Res Rev 2003; 19: 280-7
126. Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper from the American College of Physicians. Ann Intern Med 2004; 140: 650-8
127. Snow V, Aronson MD, Hornbake ER, et al. Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2004; 140: 644-9
128. Steiner G. Fibrates in the metabolic syndrome and in diabetes. Endocrinol Metab Clin North Am 2004; 33: 545-55
129. Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation 2004; 109 Suppl. III: III-50-7
130. Martin J, Krum H. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant? Drug Saf 2003; 26: 13-21
131. Johnson BF, LaBelle P, Wilson J, et al. Effects of lovastatin in diabetic patients treated with chlorpropamide. Clin Pharmacol Ther 1990; 48: 467-72
132. Appel S, Rufenacht T, Kalafsky G, et al. Lack of interaction between fluvastatin and oral hypoglycaemic agents in healthy subjects and in patients with non-insulin-dependent diabetes mellitus. Am J Cardiol 1995; 76: 29A-32A
133. Hatorp V, Hansen KT, Thomsen MS. Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. J Clin Pharmacol 2003; 43: 649-60
134. Sahi J, Black CB, Hamilton GA, et al. Comparative effects of thiazolidinediones on in vitro P450 enzyme induction and inhibition. Drug Metab Dispos 2003; 31: 439-46
135. Klotz U, Sailer D. Drug interactions: their impact on safe drug therapy in the example of the new thiazolidinedione group

(glitazone) [in German]. Arzneimittel Forschung 2001; 51: 112-7
136. Ramachandran V, Kostrubsky VE, Komoroski BJ, et al. Troglitazone increases cytochrome P-450 3A protein and activity in primary cultures of human hepatocytes. Drug Metab Dispos 1999; 27: 1194-9
137. DiTusa L, Luzier AB. Potential interaction between troglitazone and atorvastatin. J Clin Pharm Ther 2000; 25: 279-82
138. Prueksaritanont T, Vega JM, Zhao J, et al. Interactions between simvastatin and troglitazone or pioglitazone in healthy subjects. J Clin Pharmacol 2001; 41: 573-81
139. Alsheikh-Ali AA, Abourjaily HM, Karas RH. Risk of adverse events with concomitant use of atorvastatin or simvastatin and glucose-lowering drugs (thiazolidinediones, metformin, sulfonylurea, insulin and acarbose). Am J Cardiol 2002; 89: 1308-10
140. Alsheikh-Ali AA, Karas RH. Adverse events with concomitant use of simvastatin or atorvastatin and thiazolidinediones. Am J Cardiol 2004; 93: 1417-8
141. Cox PJ, Ryan DA, Hollis FJ, et al. Absorption, disposition, and metabolism of rosiglitazone, a potent thiazolidinedione insulin sensitizer, in humans. Drug Metab Dispos 2000; 28: 772-80
142. Eckland DA, Danhof M. Clinical pharmacokinetics of pioglitazone. Exp Clin Endocrinol Diab 2000; 108 Suppl. 2: S234-42
143. Freed MI, Ratner R, Marcovina SM, et al. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. Am J Cardiol 2002; 90: 947-52
144. Glazer NB, Cheatham WW. Thiazolidinediones for type 2 diabetes: no evidence exists that pioglitazone induces hepatic cytochrome P450 isoform CYP3A4 [letter]. BMJ 2001; 322: 235-6
145. Lewin AJ, Kipnes MS, Meneghini LF, et al. Effects of simvastatin on the lipid profile and attainment of low-density lipoprotein cholesterol goals when added to thiazolidinedione therapy in patients with type 2 diabetes mellitus: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2004; 26: 379-89
146. Backman JT, Kyrklund C, Neuvonen M, et al. Gemfibrozil greatly increases plasma concentrations of cerivastatin. Clin Pharmacol Ther 2002; 72: 685-91
147. Niemi M, Neuvonen PJ, Kivisto KT. Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of glimepiride. Clin Pharmacol Ther 2001; 70: 439-45
148. Niemi M, Backman JT, Neuvonen M, et al. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia 2003; 46: 347-51
149. Kajosaari LI, Backman JT, Neuvonen M, et al. Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide. Br J Clin Pharmacol 2004; 58: 390-6
150. Niemi M, Backman JT, Granfors M, et al. Gemfibrozil considerably increases the plasma concentrations of rosiglitazone. Diabetologia 2003; 46: 1319-23
151. Jones NP, Mather RA, Sautter M. Rosiglitazone treatment does not impair the triglyceride-lowering activity of fibrates in patients with type 2 diabetes mellitus [abstract]. Diabetes 2000; 49 Suppl. 1: A359, 1507-PO
152. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease. Hypertension 2001; 37: 1053-9
153. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. Diabetes Care 2004; 27: 247-55
154. Tse WY, Kendall M. Is there a role for beta-blockers in hypertensive diabetic patients? Diabet Med 1994; 11: 137-44
155. Herings RM, de Boer A, Stricker BH, et al. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. Lancet 1995; 345: 1195-8
156. Kaplan NM. Management of hypertension in patients with type 2 diabetes mellitus: guidelines based on current evidence. Ann Intern Med 2001; 135: 1079-83
157. Carey RM, Siragy HM. Newly recognized components of the renin-angiotensin system: potential roles in cardiovascular and renal regulation. Endocr Rev 2003; 24: 261-71
158. Arauz-Pacheco C, Ramirez LC, Rios JM, et al. Hypoglycaemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulfonylurea therapy. Am J Med 1990; 89: 811-3
159. Moore N, Kreft-Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. Br J Clin Pharmacol 1997; 44: 513-8
160. Girardin E, Raccah D. Interaction between converting enzyme inhibitors and hypoglycemic sulfonamides or insulin [in French]. Presse Med 1998; 27: 1914-23
161. Morris AD, Boyle DI, McMahon AD, et al. ACE inhibitor use is associated with hospitalization for severe hypoglycaemia in patients with diabetes: DARTS/MEMO Collaboration. Diabetes Care 1997; 20: 1363-7
162. Scheen AJ. Prevention of type 2 diabetes through inhibition of the renin-angiotensin system. Drugs 2004; 64 (22): 2537-65
163. The DREAM Trial Investigators . Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. Diabetologia 2004; 47: 1519-27
164. Ashcroft FM, Gribble FM. ATP-sensitive K+ channels and insulin secretion: their role in health and disease. Diabetologia 1999; 42: 903-19
165. Gribble FM, Reimann F. Differential selectivity of insulin secretagogues: mechanisms, clinical implications, and drug interactions. J Diabetes Complications 2003; 17: 11-5
166. Dhindsa P, Davis KR, Donnelly R. Comparison of the micro- and macro-vascular effects of glimepriride and gliclazide in metformin-treated patients with type 2 diabetes: a double-bind, crossover study. Br J Clin Pharmacol 2003; 55: 616-9
167. Riveline JP, Danchin N, Ledru F, et al. Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications. Diabetes Metab 2003; 29: 207-22
168. Hata N, Takano M, Kunimi T, et al. Lack of antagonism between nicorandil and sulfonylurea in stable angina pectoris. Int J Clin Pharmacol Res 2001; 21: 59-63
169. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000; 38: 41-57
170. Niemi M, Backman JT, Neuvonen M, et al. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. Clin Pharmacol Ther 2001; 69: 400-6
171. Park JY, Kim KA, Park PW, et al. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of gliclazide. Clin Pharmacol Ther 2003; 74: 334-40
172. Niemi M, Kivisto KT, Backman JT, et al. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. Br J Clin Pharmacol 2000; 50: 591-5
173. Niemi M, Backman JT, Neuvonen M, et al. Rifampicin decreases the plasma concentrations and effects of repaglinide. Clin Pharmacol Ther 2000; 68: 495-500
174. Niemi M, Backman JT, Neuvonen M, et al. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of nateglinide in healthy subjects. Br J Clin Pharmacol 2003; 56: 427-32
175. Park JY, Kim KA, Kang MH, et al. Effect of rifampicin on the pharmacokinetics of rosiglitazone in healthy subjects. Clin Pharmacol Ther 2004; 75: 157-62

176. Niemi M, Backman JT, Neuvonen PJ. Effects of trimethoprim and rifampin on the pharmacokinetics of the cytochrome P450 2C8 substrate rosiglitazone. Clin Pharmacol Ther 2004; 76: 239-49
177. Niemi M, Backman JT, Neuvonen M, et al. Effect of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. Clin Pharmacol Ther 2001; 69: 194-200
178. Hatorp V, Thomsen MS. Drug interaction studies with repaglinide: repaglinide on digoxin or theophylline pharmacokinetics and cimetidine on repaglinide pharmacokinetics. J Clin Pharmacol 2000; 40: 184-92
179. Niemi M, Kajosaari LI, Neuvonen M, et al. The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. Br J Clin Pharmacol 2004; 57: 441-7
180. Niemi M, Neuvonen PJ, Kivisto KT. The cytochrome P450 3A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. Clin Pharmacol Ther 2001; 70: 58-65
181. Niemi M, Neuvonen M, Juntti Patinen L, et al. Effect of fluconazole on the pharmacokinetics and pharmacodynamics of nateglinide. Clin Pharmacol Ther 2003; 74: 25-31
182. Sabia H, Sunkara G, Ligueros-Saylan M, et al. Effect of a selective CYP2C9 inhibitor on the pharmacokinetics of nateglinide in healthy subjects. Eur J Clin Pharmacol 2004; 60: 407-12
183. Miller AK, Di Cicco RA, Freed MI. The effect of ranitidine on the pharmacokinetics of rosiglitazone in healthy adult male volunteers. Clin Ther 2002; 24: 1062-71
184. Serrano JS, Jimenez CM, Serrano MI, et al. A possible interaction of potential clinical interest between digoxin and acarbose. Clin Pharmacol Ther 1996; 60: 589-92
185. Miura T, Ueno K, Tanaka K, et al. Impairment of absorption of digoxin by acarbose. J Clin Pharmacol 1998; 38: 654-7
186. Ben-Ami H, Krivoy N, Nagachandran P, et al. An interaction between digoxin and acarbose [letter]. Diabetes Care 1999; 22: 860-1
187. Cohen E, Almog S, Staruvin D, et al. Do therapeutic doses of acarbose alter the pharmacokinetics of digoxin? Isr Med Assoc J 2002; 4: 772-5
188. Morreale AP, Janetzky K. Probable interaction of warfarin and acarbose [letter]. Am J Health Syst Pharm 1997; 54: 1551-2
189. Schall R, Müller FO, Hundt HKL, et al. Study of the effects of miglitol on the pharmacokinetics and pharmacodynamics of warfarin in healthy males. Arzneimittel Forschung 1996; 46: 41-6
190. Kusumoto M, Ueno K, Fujimura Y, et al. Lack of kinetic interaction between digoxin and voglibose [letter]. Eur J Clin Pharmacol 1999; 55: 79-80
191. Nagai Y, Hayakawa T, Abe T, et al. Are there different effects of acarbose and voglibose on serum levels of digoxin in a diabetic patient with congestive heart failure? [letter]. Diabetes Care 2000; 23: 1703
192. Fuder H, Kleist P, Birkel M, et al. The α-glucosidase inhibitor voglibose (A0-128) does not change pharmacodynamics or pharmacokinetics of warfarin. Eur J Clin Pharmacol 1997; 53: 153-7
193. Kortboyer JM, Eckland D. Pioglitazone has low potential for drug interactions [abstract]. Diabetologia 1999; 42 Suppl. 1: A228
194. Di Cicco RA, Miller AK, Patterson S, et al. Rosiglitazone does not affect the steady-state pharmacokinetics of digoxin. J Clin Pharmacol 2000; 40: 1516-21
195. Rosenberg MA, Strange P, Cohen A. Assessment of pharmacokinetic and pharmacodynamic interaction between warfarin and repaglinide [abstract]. Diabetes 1999; 48 Suppl. 1: A356
196. Zhou H, Walter YH, Smith H, et al. Nateglinide, a new mealtime glucose regulator: lack of pharmacokinetic interaction with digoxin in healthy volunteers. Clin Drug Invest 2000; 19: 465-71
197. Sunkara G, Bigler H, Wang Y, et al. The effect of nateglinide on the pharmacokinetics and pharmacodynamics of acenocoumarol. Curr Med Res Opin 2004; 20: 41-8
198. Jetter A, Kinzig-Schippers M, Skott A, et al. Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. Eur J Clin Pharmacol 2004; 60: 165-71
199. Shon JH, Yoon YR, Kim KA, et al. Effects of CYP2C19 and CYP2C9 genetic polymorphisms on the disposition of and blood glucose lowering response to tolbutamide in humans. Pharmacogenetics 2002; 12: 111-9
200. Kirchheiner J, Bauer S, Meineke I, et al. Impact of CYP2C9 and CYP2C19 polymorphisms on tolbutamide kinetics and the insulin and glucose response in healthy volunteers. Pharmacogenetics 2002; 12: 101-9
201. Kirchheiner J, Brockmöller J, Meineke I, et al. Impact of CYP2C9 amino acid polymorphisms on glyburide kinetics and on the insulin and glucose response in healthy volunteers. Clin Pharmacol Ther 2002; 71: 286-96
202. Niemi M, Cascorbi I, Timm R, et al. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Clin Pharmacol Ther 2002; 72: 326-32
203. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol 1998; 45: 525-38
204. Niemi M, Backman JT, Fromm MF, et al. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet 2003; 42: 819-50
205. Finch CK, Chrisman CR, Baciewicz AM, et al. Rifampin and rifabutin drug interactions: an update. Arch Intern Med 2002; 162: 985-92
206. Surekha V, Peter JV, Jeyaseelan L, et al. Drug interaction: rifampicin and glibenclamide. Natl Med J India 1997; 10: 11-2
207. Greiner B, Eichelbaum M, Fritz P, et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest 1999; 104: 147-53
208. Goldstein PE, Boom A, van Geffel J, et al. P-glycoprotein inhibition by glibenclamide and related compounds. Pflugers Arch Eur J Physiol 1999; 437: 652-60
209. Odeh M, Oliven A. Doxycyline-induced hypoglycaemia. J Clin Pharmacol 2000; 40: 1173-4
210. Roberge RJ, Kaplan R, Frank R, et al. Glyburide-ciprofloxacin interaction with resistant hypoglycemia. Ann Emerg Med 2000; 36: 160-3
211. Menzies DJ, Dorsainvil PA, Cunha BA, et al. Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. Am J Med 2002; 113: 232-4
212. Lee K, Mize R, Lowenstein SR. Glyburide-induced hypoglycaemia and ranitidine. Ann Intern Med 1987; 107: 261-2
213. Kubacka RT, Antal EJ, Juhl RP. The paradoxical effect of cimetidine and ranitidine on glibenclamide pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol 1987; 23: 743-51
214. Islam SI, Masuda QN, Bolaji OO, et al. Possible interaction between cyclosporine and glibenclamide in posttransplant diabetic patients. Ther Drug Monit 1996; 18: 624-6
215. Muck W, Heine PR, Breuel HP, et al. The effect of multiple oral dosing of nimodipine on glibenclamide pharmacodynamics and pharmacokinetics in elderly patients with type-2 diabetes mellitus. Int J Clin Pharmacol Ther 1995; 33: 89-94
216. Boni JP, Cevallos WH, DeCleene S, et al. The influence of bromfenac on the pharmacokinetics and pharmacodynamic responses to glyburide in diabetic subjects. Pharmacotherapy 1997; 17: 783-90

217. Gleiter CH, Schreeb KH, Freudenthale S, et al. Lack of interaction between thioctic acid, glibenclamide and acarbose. Br J Clin Pharmacol 1999; 48: 819-25
218. van Giersbergen PLM, Treiber A, Clozel M, et al. In vivo and in vitro studies exploring the pharmacokinetic interaction between bosentan, a dual endothelin receptor antagonist, and glyburide. Clin Pharmacol Ther 2002; 71: 253-62
219. Martin DE, DeCherney GS, Ilson BE, et al. Eprosartan, an angiotensin II receptor antagonist, does not affect the pharmacodynamics of glyburide in patients with type II diabetes mellitus. J Clin Pharmacol 1997; 37: 155-9
220. Feely J, Collins WC, Cullen M, et al. Potentiation of the hypoglycaemic response to glipizide in diabetic patients by histamine H2-receptor antagonists. Br J Clin Pharmacol 1993; 35: 321-3
221. Chidester PD, Connito DJ. Interaction between glipizide and cyclosporine: report of two cases. Transplant Proc 1993; 25: 2136-7
222. Sagedal S, Asberg A, Hartmann A, et al. Glipizide treatment of post-transplant diabetes does not interfere with cyclosporine pharmacokinetics in renal allograft recipients. Clin Transplant 1998; 12: 553-6
223. Kihara Y, Otsuki M. Interaction of gliclazide and rifampicin [letter]. Diabetes Care 2000; 23: 1204-5
224. Abad S, Moachon L, Blanche P, et al. Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. Br J Clin Pharmacol 2001; 52: 456-7
225. Holstein A, Plaschke A, Hammer C, et al. Characteristics and time course of severe glimepiride- versus glibenclamide-induced hypoglycaemia. Eur J Clin Pharmacol 2003; 59: 91-7
226. Klepser TB, Kelly MW. Metformin hydrochloride: an antihyperglycemic agent. Am J Health Syst Pharm 1997; 54: 893-903
227. Howlett HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. Drug Saf 1999; 20: 489-503
228. Somogyi A, Stockley C, Keal J. Reduction of metformin renal tubular secretion by cimetidine in man. Br J Clin Pharmacol 1987; 23: 545-51
229. Richardt D, Rosmarin C, Havlik I, et al. No effect of miglitol on the oral bioavailability of single-dose phenytoin in healthy males. Clin Drug Invest 1997; 13: 171-4
230. Farley-Hills E, Sivasankar R, Martin M. Fatal liver failure associated with pioglitazone [letter]. BMJ 2004; 329: 429
231. Scheen AJ, Luyckx FH. Liver disease in obesity. Best Pract Res Clin Endocrinol Metab 2002; 16: 703-16
232. Jick SS, Stender M, Myers MW. Frequency of liver disease in type 2 diabetic patients treated with oral antidiabetic agents. Diabetes Care 1999; 22: 2067-71
233. Belcher G, Lambert C, Edwards GC, et al. Results of liver safety testing in 3713 type 2 diabetic patients treated for one year in double blind controlled trials with pioglitazone, metformin or gliclazide [abstract]. Diabetologia 2003; 4 Suppl. 2: A291
234. Lebovitz HE, Kreider M, Freed MI. Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care 2002; 25: 815-21
235. Scheen AJ. Combined thiazolidinedione-insulin therapy: should we be concerned about safety? Drug Saf 2004; 27: 841-56
236. Yamazaki H, Suzuki M, Tane K, et al. In vitro inhibitory effects of troglitazone and its metabolites on drug oxidation activities of human cytochrome P450 enzymes: comparison with pioglitazone and rosiglitazone. Xenobiotica 2000; 30: 61-70
237. Kaplan B, Friedman G, Jacobs M, et al. Potential interaction of troglitazone and cyclosporine. Transplantation 1998; 65: 1399-400
238. Glazer NB, Cheatham WW. Thiazolididiones for type 2 diabetes: no evidence exists that pioglitazone induces hepatic cytochrome P450 isoform CYP3A4 [letter]. BMJ 2001; 322: 252-3
239. Carey R, Liu Y. Pioglitazone does not markedly alter oral contraceptive or hormone replacement pharmacokinetics [abstract]. Diabetes 2000; 49 Suppl. 1: A340-1
240. Baldwin SJ, Clarke SE, Chenery RJ. Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. Br J Clin Pharmacol 1999; 48: 424-32
241. Rao MN, Mullangi R, Katneni K, et al. Lack of effect of sucralfate on the absorption and pharmacokinetics of rosiglitazone. J Clin Pharmacol 2002; 42: 670-5
242. Thompson KA, Miller AK, Inglis AML, et al. Rosiglitazone does not markedly alter CYP3A4-mediated drug metabolism [abstract]. Diabetologia 1999; 42 Suppl. 1: A227
243. Harris RZ, Inglis AML, Miller AK, et al. Rosiglitazone has no clinically significant effect on nifedipine pharmacokinetics. J Clin Pharmacol 1999; 39: 1189-94
244. Inglis A, Miller A, Culkin K, et al. Lack of effect of rosiglitazone on the pharmacokinetics of oral contraceptives in healthy female volunteers. J Clin Pharmacol 2001; 41: 683-90
245. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. Clin Pharmacokinet 2002; 41: 471-83
246. Plum A, Müller LK, Jansen JA. The effects of selected drugs on the in vitro protein binding of repaglinide in human plasma. Methods Find Exp Clin Pharmacol 2000; 22: 139-43
247. Bidstrup TB, Bjornsdottir I, Sidelman UG, et al. CYP2C8 and CYP3A4 are the principal enzymes involved in the human in vitro biotransformation of the insulin secretagogue repaglinide. Br J Clin Pharmacol 2003; 56: 305-14
248. Niemi M, Leathart JB, Neuvonen M, et al. Polymorphism in CYP2C8 is associated with reduced plasma concentrations of repaglinide. Clin Pharmacol Ther 2003; 74: 380-7
249. Schwietert R, Wemer J, Jonkman JHG, et al. No change in repaglinide pharmacokinetics with cimetidine co-administration [abstract]. Eur J Clin Pharmacol 1997; 52: A140
250. Schwietert R, Wemer J, Jonkman JHG, et al. Co-administration of repaglinide does not affect digoxin pharmacokinetics [abstract]. Eur J Clin Pharmacol 1997; 52: A140
251. Weaver ML, Orwig BA, Rodriguez LC, et al. Pharmacokinetics and metabolism of nateglinide in humans. Drug Metab Dispos 2001; 29: 415-21
252. Kirchheiner J, Meineke I, Müller G, et al. Influence of CYP2C9 and CYP2D6 polymorphisms on the pharmacokinetics of nateglinide in genotyped healthy volunteers. Clin Pharmacokinet 2004; 43: 267-78
253. Anderson D, Shelley S, Crick N, et al. A 3-way crossover study to evaluate the pharmacokinetic interaction between nateglinide and diclofenac in healthy volunteers. Int J Clin Pharmacol Ther 2002; 40: 457-64
254. Anderson D, Shelley S, Crick N, et al. No effect of the novel antidiabetic agent nateglinide on the pharmacokinetics and anticoagulant properties of warfarin in healthy volunteers. J Clin Pharmacol 2002; 42: 1358-65

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