

Combination therapy with oral hypoglycemic agents: Rationale and principles

AMIR K. HANNA, MB, BCH, FRCPC, FACP

The objective of this inaugural issue of *Endocrinology Rounds* is to review the impact of intensive and early glucose control on the complications of diabetes, understand the characteristics of the different classes of oral hypoglycemic agents, highlight the benefits of combination therapy with oral hypoglycemic agents, and provide an overview of recent combination therapy studies.

Studies in people with type 1 and 2 diabetes¹⁻³ have demonstrated that intensive treatment of hyperglycemia results in significant reduction in microvascular complications and a tendency for decreased macrovascular disease. Epidemiological analyses of the United Kingdom Prospective Diabetes Study (UKPDS)⁴ found a continuous relationship between glucose levels and both micro- and macrovascular disease.

The DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group) study⁵ followed up most of the original cohort of the DCCT for 4 years after the original results were analyzed. The group initially assigned to intensive treatment continued to show significantly less microvascular complications when compared to the conventional treatment group, even though the difference in HbA_{1c} values between the 2 groups became much smaller. In the Kumamoto 8-year update study, differences in HbA_{1c} between the intensive and conventional groups, seen at the end of the first 6 years of the study, were maintained. Continuing protection from microvascular complications was noted.⁶

Management protocols derived from The Clinical Practice Guidelines for the Management of Diabetes in Canada⁷ recommend a step-wise approach to glucose control in people with type 2 diabetes. This approach commences with life-style changes and is followed by oral agent monotherapy, combinations of oral agents, and finally, adding or substituting insulin. Moving from one step of treatment to the next is recommended when target levels of blood glucose are not attained after a waiting period of 2 to 4 months. This approach, however, accepts treatment failure and tolerates the detrimental effects of glucose toxicity on insulin secretion and sensitivity.

A new paradigm of early utilization of combination therapy has, therefore, been suggested. It is aimed at attaining ideal blood glucose levels early on in the course of therapy. This approach is followed by efforts to maintain these ideal levels with frequent measurements of pre- and postprandial glucose levels, HbA_{1c}. Target levels of these variables are based on those found in people without diabetes (eg, a HbA_{1c} level that is <6%). This approach has the following benefits:

- it targets the different pathogenetic factors contributing to hyperglycemia, (ie, insulin resistance, impaired beta cell function, and increased hepatic glucose production);
- it uses sub-maximal doses of different oral agents, decreasing the possible side effects of such medications;
- it avoids the effects of glucose toxicity.



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St. Michael's Hospital
6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

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There are two studies – Action to Control Cardiovascular Disease in Diabetes (ACCORD) and the VA Diabetes Trial^{8,9} – that are now evaluating the effect of attaining normal glycemia ($\text{HbA}_{1c} < 6\%$), among other interventions, on the occurrence of macrovascular complications in patients with type 2 diabetes.

Characteristics of the different classes of oral hypoglycemic agents

Insulin secretagogues

Insulin secretagogues act by binding to the different sulfonylurea receptor sites on the plasma membrane of beta cells in the pancreatic islets. The resulting closure of the K_{ATP} channels leads to membrane depolarization, opening of the calcium channels, and influx of calcium, resulting in insulin secretion. This group of drugs is utilized in an attempt to correct the quantitative (overall decreased insulin secretion in response to hyperglycemia) and qualitative (absent first phase insulin secretion) abnormalities of insulin secretion in type 2 diabetes.

Sulfonylureas increase insulin secretion; however, only some members of this class partially restore first phase insulin excursion. This group of drugs is usually well tolerated, effective in lowering blood glucose, but has a 1%-10% yearly secondary failure rate. Hypoglycemia and weight gain are the main side effects, the magnitude of which vary among different members of this class. Gliclazide and glimepiride tend to be associated with less hypoglycemia and weight gain.^{10,11}

Meglitinide analogues

These drugs represent a new family of insulin secretagogues. Structurally, they are non-sulfonylurea agents. They are absorbed rapidly, stimulate insulin release within a few minutes, have a more potent effect on enhancing first phase insulin secretion, are rapidly metabolized in the liver, and are excreted mainly in bile. The meglitinide analogues are short-acting. They appear to lower postprandial glucose levels more than the sulfonylureas and are associated with less hypoglycemia. Glucose control, as measured by HbA_{1c} , is equivalent to the sulfonylureas and metformin. These drugs are therefore more suitable for patients with type 2 diabetes who have a variable lifestyle and elevated postprandial glucose levels.¹²⁻¹⁶ Nateglinide is a phenylalanine derivative. In a study in a group of non-diabetic volunteers that compared nateglinide 120 mg to repaglinide 2 mg taken 10 min before food, nateglinide resulted in a more rapid and short-lived stimulation of insulin secretion, resulting in lower meal-related glucose excursions.¹⁷ Repaglinide is available in Canada, while nateglinide, which is available in the United States and other countries, is not yet available in Canada. The recommended dose of repaglinide is 0.5 to 4 mg, up to 4 times a day; nateglinide is recommended in a dosage of 120 mg tid, taken shortly before meals.

Insulin sensitizers

The thiazolidinediones: pioglitazone and rosiglitazone

Pioglitazone and rosiglitazone are members of the thiazolidinedione family, a group of insulin sensitizing agents that enhance sensitivity to insulin in adipose tissue, striated muscle and, to a lesser extent, in the liver. They decrease hepatic glucose production and increase insulin-mediated glucose uptake. The mechanism of action is not fully elucidated. Both agents are known to bind to the nuclear receptor PPAR- γ (peroxisome proliferator-activated receptor-gamma), which regulates the transcription of several genes involved in insulin-mediated glucose uptake in peripheral tissues, bringing about increased glucose transporter translocation (GLUT-4) to the cell membrane. Their effect appears to be achieved primarily by direct action on fat cells. Both drugs, therefore, amplify insulin action and reduce insulin resistance.¹⁸⁻²⁰

The glucose-lowering effect of these drugs is similar to the sulfonylureas. In patients naive to oral agents, the decrease in HbA_{1c} ranges between 0.8% and 1.9%, depending on the dose used. In a group of patients with type 2 diabetes previously treated with other oral hypoglycemic agents, the decrease in HbA_{1c} ranged between 0.3 and 0.9%.²¹⁻²⁵ Thiazolidinediones are slow to reach their maximum therapeutic effect, taking between 8-12 weeks to do so. In a study that compared rosiglitazone with pioglitazone in patients with type 2 diabetes previously treated with troglitazone, there was no difference in glycemic control as measured by HbA_{1c} .²⁴ Other characteristics of these drugs are shown in Table 1.

Side effects of pioglitazone and rosiglitazone

Side effects occur in a small number of patients and have resulted in <1% withdrawal from clinical studies. Edema was reported in about 5%-15% of patients treated with pioglitazone in monotherapy and with different combinations.³⁹ Edema tended to be more severe in combination with insulin and sulfonylureas as compared to monotherapy. About 1%-6% of patients on rosiglitazone experience edema.^{24,64} The differences in edema incidence could be related to design of the studies mentioned. In patients with history of CHF or NYHA class 3 and 4, the risk of heart failure is such that these drugs should not be used. Decreased hemoglobin of 3 to 10 gm/L was noted in some studies.^{24,39} An average 0.7-3.5 kg weight gain has been noted, related to both increased fat mass and fluid retention. A higher degree of weight gain was noted when these drugs were combined with insulin.^{24,33} In long-term use, no significant hepatic toxicity has been observed.

Recommendations for pioglitazone and rosiglitazone use

Both drugs are recommended in patients with type 2 diabetes who are not adequately controlled or unable to

Table 1: Characteristics of the thiazolidinediones (pioglitazone, rosiglitazone)

- There is evidence of preservation of islet cell insulin content and improved beta cell function.^{26,28}
- Fat distribution studies suggest a decrease in visceral fat in the context of overall increased fat mass related to increased peripheral fat. There was a significant reduction in waist/hip ratio in a 26-week study with rosiglitazone.^{24,29,30}
- A slight decrease (2.3 mm Hg) in diastolic blood pressure was noted with rosiglitazone compared to baseline, and in systolic blood pressure with pioglitazone compared to acarbose (10 mm Hg decrease with pioglitazone, compared to 1.5 mm Hg decrease with acarbose).^{31,32}
- There is reduction in free fatty acid levels²⁴ and a favorable effect on lipid parameters with both pioglitazone and rosiglitazone, reducing the LDL/HDL ratio. In studies with pioglitazone, there was a tendency towards more reduction in triglyceride levels as compared to rosiglitazone.^{24,33} However, there are no head to head comparisons between these two drugs, making a definitive conclusion hard to ascertain.
- There is no evidence of clinically significant drug interactions with other oral hypoglycemic agents, oral contraceptives, nifedipine, digoxin, ranitidine, or warfarin.^{33,34}
- Studies with rosiglitazone show that its pharmacokinetics are not altered in renally impaired patients or those on hemodialysis; as well, the pharmacokinetics of pioglitazone are not altered in moderate to severe renally impaired patients. Thus, there is no need to change the drug dosage in patients with impaired renal function.^{33,37}
- Preliminary studies with rosiglitazone show a tendency towards decreased albumin excretion rate and albumin/creatinine ratio.^{24,38} This, however, has not yet been verified in long-term controlled studies.

tolerate their current oral hypoglycemic therapy. In patients in whom other oral hypoglycemic therapies are contraindicated, the thiazolidinediones provide an effective and safe alternative. I feel that the present data⁴⁰ justify the addition of a thiazolidinedione in patients who are not meeting treatment targets while on maximum doses of combination sulfonylurea and metformin. It is also my opinion that in certain patients who require large amounts of insulin – especially if they are not attaining glycemic targets – the addition of a thiazolidinedione could improve glucose parameters and reduce insulin dosage. This combination, however, should be used with extreme caution because of the possibility of accelerated edema, weight gain, and congestive heart failure. The recommended doses for pioglitazone are 15, 30, or 45 mg once daily; for rosiglitazone, it is 4 mg once or twice per day or 8 mg once daily.

Contraindications

- Abnormal liver function tests: AST > 2.5 times normal is a contraindication to starting patients on this group of drugs

- Patients with a history of congestive heart failure, or in the NYHA class 3 and 4 should not be given thiazolidinediones.
- Pregnancy: fertility may be restored in patients with polycystic ovary syndrome (PCO) as insulin resistance decreases. Precautions to prevent pregnancy should be discussed with the patient and documented until further experience is gained with these drugs.

Metformin

Metformin acts on the liver by reducing hepatic glucose production. It suppresses gluconeogenesis mainly by potentiating the effects of insulin, reducing hepatic extraction of certain substrates (eg, lactate), and opposing the effects of glucagon.⁴¹ Insulin-stimulated glucose uptake into skeletal muscles is enhanced mainly as a result of increased movement of glucose transporters into the cell membrane.⁴² Metformin suppresses fatty acid oxidation and reduces hypertriglyceridemia. A meta-analysis of 9 randomized controlled trials compared metformin with sulfonylurea. Glucose was reduced by 2 mmol/L and HbA_{1c} by 0.9% compared to placebo, with no significant weight change. These results were similar to the sulfonylureas, except in terms of body weight (an increase of 1.7 kg with sulfonylureas, compared to a 1.2 kg weight loss in metformin-treated subjects).⁴³

Alpha-glucosidase inhibitors

The alpha-glucosidase inhibitors inhibit the effects of intestinal enzymes responsible for carbohydrate absorption. Alpha-glucosidases are enzymes located on the brush border of the small intestine where they break down oligosaccharides and disaccharides into monosaccharides, which are then absorbed in the proximal jejunum. They do not directly affect beta cells and do not cause hypoglycemia. They attenuate postprandial glycemia. There is minimal absorption of alpha-glucosidase inhibitor from the gut, about 2%-3%; the rest remains enteric.⁴⁴ Both acarbose and miglitol reduce glucose less effectively than glyburide (0.75% compared to 1%) and cause more gastrointestinal side-effects (flatulence seen twice as much in the treatment group versus the control groups). They do not cause weight gain or hypoglycemia.⁴⁵ Acarbose is available in Canada, while miglitol is not.

Both acarbose and miglitol are given at 50-100 mg tid, taken with the first bite of the meal. Starting with a low dose (25 mg once daily), and gradually increasing the dose, seems to reduce the gastrointestinal side effects.

Combination studies

Primary combination therapy

In a study by Herman et al, 56 newly diagnosed patients with type 2 diabetes were randomized to either to metformin or glyburide monotherapy, or a combination.

Follow-up for 6 months showed a decrease in fasting plasma glucose (FPG) by 3.2 mmol/L and in HbA_{1c} by 1.5% in all groups. Weight increased by 3.1 kg in the glyburide group, but stayed constant in the others.⁴⁶

A second study by Haupt et al,⁴⁷ combining metformin with a maximum dose of sulfonylurea, in patients who failed monotherapy, resulted in a decrease in fasting plasma glucose by 2.8 mmol/L, postprandial glucose by 4.1 mmol/L, and HbA_{1c} by 1.9%.⁴⁷

In a third study,⁴⁸ 806 patients with newly diagnosed type 2 diabetes who did not attain optimal control with life-style changes were randomized to placebo, glyburide, metformin, and two fixed combinations of metformin/glyburide (M/G): 250/1.25 mg and 500/2.5 mg. Final doses for each active treatment group were: 5.3 mg glyburide; 1317 mg metformin, and 557/2.8 mg and 818/4.1 mg M/G, respectively. Decrease in HbA_{1c} was significantly greater with the fixed combinations (1.48% and 1.53%, respectively), compared with placebo (0.21%), ($P<0.001$ for both); glyburide: 1.24%, ($P<0.02$ for M/G 250/1.25, and $P<0.005$ for M/G 500/2.5) and metformin: 1.03% ($P<0.001$ for both) at week 20. Sixty-five to 70% of patients on the fixed combinations reached HbA_{1c} <7%, significantly more than other treatment arms.

Combination therapy with oral agents after failure with monotherapy

Glyburide + metformin

In a study by DeFronzo et al, 632 patients were treated with diet, or diet + a sulfonylurea. Open label glyburide was stopped. Patients were randomized to: glyburide (n=209), metformin (n=210), or both medications (n=213). Fasting plasma glucose decreased by 0.9 mmol/L in the glyburide group, 0.4 mmol/L in the metformin group, and by 3.4 mmol/L in the group receiving the combination of both drugs ($P<0.001$). HbA_{1c} decreased by 0.2% in the glyburide group, 0.4% in the metformin group, and 1.7% in the combination therapy group ($P<0.001$). Body weight remained the same with glyburide, decreased by 3.8 kg with metformin, and by 0.4 kg with the combination.⁴⁹

Nateglinide + metformin

701 patients with type 2 diabetes were randomized to nateglinide 120 mg tid alone, metformin 500 mg tid alone, or a combination of nateglinide 120 mg and metformin 500 mg tid after a washout period. They were followed for 24 weeks. The results showed that HbA_{1c} and FPG decreased more with combination therapy as compared to monotherapy ($P<0.0001$). HbA_{1c} was reduced by 1.4% in the combination group compared to 0.5% and 0.8% in the

nateglinide and metformin groups, respectively. Fasting plasma glucose was reduced by 2.4 versus 1.6 and 2.4 mmol/L, respectively. The area under the curve of glucose excursion was significantly lower with both nateglinide and combination therapy compared to placebo and metformin.⁵⁰

Repaglinide + metformin

83 patients with type 2 diabetes who failed to achieve treatment targets while on treatment with metformin (HbA_{1c} >7.1%) were randomized to metformin (n=27), repaglinide (n=29), or a combination of both (n=27). The same metformin dose was continued in patients receiving mono or combination therapy; however, repaglinide was adjusted over a 4-8 week titration period. Patients were followed for a period of 3 months after reaching the final repaglinide dose. Fasting plasma glucose decreased by 2.2 mmol/L ($P<0.0003$) and HbA_{1c} by 1.4% in the combination therapy group ($P<0.0016$); 60% of the patients receiving combination therapy reached HbA_{1c} <7% compared to only 20% in either monotherapy groups.⁵¹

Other combination studies with repaglinide

Combination studies done with metformin, troglitazone, rosiglitazone, pioglitazone and insulin showed a reduction in HbA_{1c} by 1.3% to 1.7%.⁵⁵⁻⁵⁹ Missed-lunch studies have shown less hypoglycemia when compared to glyburide

Rosiglitazone and pioglitazone combination studies

Studies combining rosiglitazone or pioglitazone with sulphonylureas, metformin, and insulin showed additional glucose lowering. Fasting plasma glucose and HbA_{1c} showed significant decline. HbA_{1c} declined by 1.6% to 1.7% compared to placebo.⁵⁵⁻⁵⁹ A recent study of triple therapy using troglitazone in patients who fail to attain optimal glycemic control with maximum doses of metformin and glyburide, showed an average decrease in HbA_{1c} of 1.4% compared to placebo.⁴⁰ At the present time, the glitazones are not currently indicated for use in combination with insulin in Canada.

Alpha-glucosidase inhibitors

Combination therapy of acarbose^{60,61} and miglitol⁶² with sulfonylureas, metformin, and insulin results in a reduction in HbA_{1c} of 0.5% to 1.4%.

Conclusion

Glycemic control in patients with type 2 diabetes should aim at normalization of glucose parameters: fasting, postprandial glucose and HbA_{1c}.

Table 2: Rationale for targeting postprandial glucose levels

- Postprandial glucose levels correlate better with HbA_{1c} values
- There is a correlation between postprandial glucose and cardiovascular disease (The DECODE study⁶³).
- The availability of interventions targeting postprandial glucose control: dietary interventions (high soluble fiber foods, foods with low glycemic index), insulin secretagogues of the meglitinide group, and rapid-acting insulin analogues

Early introduction of combination therapy with oral agents is recommended, rather than the stepwise approach presently advocated in the Clinical Practice Guidelines. Target levels of control should be the same as those found in people without diabetes. Failure of combination oral agents to attain such targets is an indication for additional therapy or substitution of insulin. Postprandial glucose levels correlate with HbA_{1c} and cardiovascular disease better than fasting glucose levels (Table 2). Targeting postprandial glucose levels is made possible by interventions that improve first phase insulin secretion, delay carbohydrate absorption, or provide rapid acting insulins.

Amir K. Hanna, MB, BCh, FRCPC, FACP, is an Associate Professor, Department of Medicine, University of Toronto, and Director, Diabetes Clinic, St. Michael's Hospital, Toronto, Ontario

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive therapy of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329: 977-986.
2. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28:103-117.
3. UKPDS Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853.
4. Stratton IM, Adler AL, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of Type 2 Diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405-412.
5. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 2000;342(6):381-389.
6. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto study on optimal diabetes control in diabetic patients. *Diabetes Care* 2000;23(suppl 2):B21-9.
7. Meltzer S, Leiter L, Daneman D, et al. 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada. *CMAJ* 1998; 159 Suppl 8:S1-29.
8. Action to Control Cardiovascular Disease in Diabetes (ACCORD) Study Protocol 2.
9. Duckworth WC, McCarren M, Abaira C, Veterans Affairs Diabetes Trial (VADT), Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care* 2001;24(5):942-945.
10. Tessier D, Dawson K, Tetrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. *Diabet Med* 1994;11(10):974-80.
11. Holstein P, et al. Glimepiride less hypoglycemia than glyburide. *Diabetologia* 2000;43:A40.
12. Malaisse WJ. Stimulation of insulin release by non-sulfonylurea hypoglycemic agents: the meglitinide family. *Horm Metab Res* 1995; 27:263-266.
13. Wolffenbuttel BHR, Landgraf R, on behalf of the Dutch and German Repaglinide Study Group. A 1-year multi-center randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care* 1999;22:463-467.
14. Nateglinide: A structurally novel insulin secretion agent. *Drugs of Today* 2001;37(suppl F)1-16.
15. Damsbo P, Clauson P, Marbury TC, et al. A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well controlled type 2 diabetic patients. *Diabetes Care* 1999;22:789-794.
16. Kristensen JS, Frandsen KB, et al. The frequency of severe hypoglycemia is reduced with repaglinide treatment compared with sulphonylurea treatment. *Eur J Endocrinol* 1999;140(Suppl 1) 19:Abstract 57.
17. Kalbag, JB, Walter, YH, Nedelman, JR, et al. Mealtime glucose regulation with nateglinide in healthy volunteers: comparison with repaglinide and placebo. *Diabetes Care* 2001;24(1):73-77.
18. Lehmann JM, Moore LB, Smith-Oliver TA, et al. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor. *J Biol Chem* 1995;270:12953-12956
19. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes* 1996;45:1661-1669.
20. Willson TM, Brown PJ, Sternbach DD, et al. The PPARs: from orphan receptors to drug discovery. *J Med Chem* 2000; 43:527-550.
21. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. *Diabetes Care* 2000;23:1605-1611.
22. Raskin P, Rappaport EB, Cole ST, et al. Rosiglitazone short-term monotherapy lowers fasting and postprandial glucose in patients with type II diabetes. *Diabetologia* 2000;43:278-284.
23. Nolan JJ, Jones NP, Patwardhan R, et al. Rosiglitazone taken once daily provides effective glycemic control in patients with Type 2 diabetes mellitus. *Diabet Med* 2000;17:287-294.
24. Lebovitz HE, Dole J, Patwardhan R, et al. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2001;86:280-288.
25. Khan MA, St Peter JV, Neafus KL, et al. A prospective, randomized comparison of the metabolic effects of pioglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes* 2001;50(Suppl.2):A119.
26. Matthews DR, Bakst A, Weston WM, et al. Rosiglitazone decreases insulin resistance and improves beta-cell function in patients with type 2 diabetes. *Diabetologia* 1999;42(Suppl 1): Abstract 858.
27. Rosenstock J, for the pioglitazone HCl study group. Improved insulin sensitivity and beta cell response with pioglitazone therapy suggested by HOMA analysis. *Diabetologia* 2000; 43(Suppl 1):A192.
28. Jones NP, et al. Rosiglitazone reduces plasma insulin and its precursors while decreasing glycemia in type 2 diabetes. *Diabetes* 1999;48 (Suppl 1):Abstract 859.
29. Kelly IE, Han TS, Walsh K, et al. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. *Diabetes Care* 1999;22:288-293.
30. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in patients with type 2 diabetes mellitus (T2DM). *Diabetes* 2000;49(Suppl.1):A299.
31. St John Sutton M, Dole J, Rappaport EB. Rosiglitazone does not adversely affect cardiac structure or function in patients with type 2 diabetes. *Diabetes* 1999;42(Suppl 1):A102.
32. Scherbaum W, Goke B, for the German Pioglitazone Study Group, Dusseldorf and Munich, Germany. Pioglitazone reduces blood pressure in patients with type 2 diabetes mellitus. *Diabetes* 2001;50 (Suppl 2):A462.
33. Avandia (rosiglitazone maleate) Product Monograph, CPS.
34. Crijns-Kortboyer J, Eckland D. Pioglitazone has low potential for drug interaction. *Diabetologia* 1999;42(Suppl 1):A228.
35. Chapelsky MC, Thompson K, Miller A. Effect of renal impairment on the pharmacokinetics of rosiglitazone (RSG). *Clin Pharmacol Ther* 1999;65:185.
36. Thompson K, Zussman B, Miller A. Pharmacokinetics of rosiglitazone are unaltered in hemodialysis patients. *Clin Pharmacol Ther* 1999;65:186.

37. Edwards G, Eckland D. Pharmacokinetics of pioglitazone in patients with renal impairment. *Diabetologia* 1999;42(Suppl 1):A228.
38. Bakris G, Weston WM, Rappaport EB, et al. Rosiglitazone produces long-term reductions in urinary albumin excretion in type 2 diabetes. *Diabetologia* 1999;42(Suppl 1):A865.
39. Aronoff SL. Adverse events with pioglitazone HCL. *Diabetes* 2000; 49(Suppl 1):A340.
40. Yale JF, Valiquett TR, Ghazzi MN, et al. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo controlled trial. *Ann Intern Med* 2001; 134:737-741.
41. Wiernsperger, NF, Bailey, CJ. The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. *Drugs* 1999; 58(Suppl 1): 31-39.
42. Klip, A, Leiter, LA. Cellular mechanism of action of metformin. *Diabetes Care* 1990;13 (6):696-704. Review.
43. Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta-analysis. *Diabetes Care* 1999;22(1):33-37.
44. Caspry, WF. Sucrose-malabsorption in man after ingestion of alpha-glucosidase inhibitor. *Lancet* 1978;1:1231-1233.
45. Segal, P., Feig PU, Scherthner, G, et al. The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone. *Diabetes Care* 1997; 20(5):687-691.
46. Hermann LS, Bitzen PO, Kjellstrom T, et al. Comparative efficacy of metformin and glibenclamide in patients with non-insulin-dependent diabetes mellitus. *Diabete Metab* 1991;17:201-208.
47. Haupt E, Knick B, Koschinsky T, et al. Oral antidiabetic therapy with sulphonylureas and metformin. *Diabetes Metab* 1991;17:224-231.
48. Garber A, Davidson J, Mooradian A, et al. Effect of metformin/glyburide tablets on HbA_{1c} in first-line treatment of type 2 diabetes. *Diabetes* 2000; 49(suppl 1): Abstract 432- P
49. DeFronzo R, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* 1995;333(9):541-549.
50. Horton ES, Clinkingbeard C, Gatlin 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(11):1660-1665.
51. 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;22:119-122.
52. Jovanovic L, Jain R, Greco S, et al. Repaglinide/pioglitazone combination therapy in type 2 diabetes [Abstract]. *Diabetes* 2001; 50(Suppl.2):Abstract 1830-PO.
53. Landin-Olsson M, Brogard JM, et al. The efficacy of repaglinide administered in combination with bedtime NPH-insulin in patients with type 2 diabetes [Abstract]. *Diabetes* 1999;46(Suppl 1):A117. Abstract 0503.
54. Eriksson JG, Brogard JM, et al. The safety of repaglinide administered in combination with bedtime NPH-insulin in patients with type 2 diabetes [Abstract]. *Diabetes* 1999;48(Suppl 1):A360. Abstract 1575.
55. Schneider R, Egan J, Houser V. Combination therapy with pioglitazone and sulfonylurea in patients with type 2 diabetes. *Diabetes* 1999;48(Suppl 1): A106.
56. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther* 2000; 22:1395-1409.
57. Rubin C, Egan J, Schneider R. Combination therapy with pioglitazone and insulin in patients with type 2 diabetes. *Diabetes* 1999; 48(Suppl 1):A110.
58. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. *JAMA* 2000;283:1695-1702.
59. Gomis R, Jones NP, et al. Low-dose rosiglitazone enhances glycaemic control when combined with sulphonylureas in type 2 diabetes. Poster presentation at the 59th American Diabetes Association Annual Meeting; June 19-22, 1999; San Diego, California: Poster 266
60. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44) *Diabetes Care* 1999;22(6): 960-964.
61. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med* 1994; 121(12):928-935.
62. Chiasson JL, Naditch L. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care* 2001; 24(6):989-94.
63. Balkau B. The DECODE study. Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe. *Diabetes Metab* 2000; 26(4):282-6.
64. Phillipis LS, Grunberger G, Miller E, et al. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with Type 2 diabetes. *Diabetes Care* 2001;24:308-315.

Abstract of Interest

Nateglinide is safe and efficacious in lowering postprandial blood glucose in Type 2 diabetic patients with various degree of renal function.

TOMOFUSA ISHII, TETSUYA YAMAKITA, KEIKO YAMAGAMI, ET AL. OSAKA, JAPAN.

Impaired renal function results in reduced excretion of most oral hypoglycemic agents (OHAs) and its metabolites, increasing the duration of drug action and increasing the risk of hypoglycemia. Nateglinide (NAT) is a novel OHA that acts by stimulating the secretion of insulin but is unique among OHAs in its short biological half-life and largely nonrenal route of excretion, so it may be safe and efficacious in lowering postprandial blood glucose in Type 2 diabetes even with renal impairment. We examined this issue in 8 inpatients with Type 2 diabetes with various degrees of renal function (male/female: 4/4, age: 64±6 years, BMI 22.3±1.9 kg/m², HbA_{1c} 7.8±1.3%, fasting plasma glucose 169±54 mg/dl, creatinine clearance [CLCR] 41.8±16.2 ml/min, 71.5 to 21.6 ml/min, mean±SD), who were not administered any OHAs. Participants were examined on 2 consecutive days without (Day 1) or with (Day 2) an administration of NAT (90 mg) before a standardized breakfast, and 6 days after the NAT therapy (270 mg/day, 3 times before meals) (Day 7). Postprandial glucose, concentrations of insulin, C-peptide, plasma NAT and its major metabolite (M1) were measured every hour on Day 1 and Day 2. Postprandial glucose was lower and the concentrations of insulin and C-peptide were higher on Day 2 compared with those on Day 1 (*p*<0.05, respectively). The ratio of Day 2 to Day 1 for insulin concentrations had no relation to CLCR (*r*=0.09). The concentrations of NAT (4.4±0.9 microg/ml) and M1 (1.1±0.6 microg/ml) peaked 1 hour after an administration of NAT in all patients, and area under the curve for the concentrations of NAT and M1 had no relation to CLCR (*r*=0.08 and *r*=1.82, respectively). There observed no significant increase in the concentration of fasting insulin on Day 7 compared with that on Day 1 and Day 2 (4.4±1.2, 4.2±1.4 and 4.8±1.6 microU/ml, respectively), and no accumulation of plasma NAT or M1 early in the morning on Day 7. It is concluded that NAT is safe and efficacious in lowering postprandial blood glucose in Type 2 diabetes with mild-to-moderate renal impairment.

Upcoming Meetings

1-3 February, 2002

American Diabetes Association

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San Francisco, California

CONTACT: ADA Meeting Services Department

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E-mail: meetings@diabetes.org

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American Diabetes Association 62nd Annual Meeting and Scientific Sessions

San Francisco, California

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2-5 October 2002

Canadian Diabetes Association and the Canadian Society of Endocrinology Metabolism

Professional Conference and Annual Meetings

Vancouver, British Columbia

CONTACT: Helena Miekus

Tel: 416 363-0177 Ext. 571

Fax: 416 363-7465

E-mail: helena.miekus@diabetes.ca

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