

Case Report: Treating type 2 diabetes

Using four oral hypoglycemic drugs

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Type 2 diabetes is a progressive disorder. Although oral monotherapy is often successful initially, it is associated with a high secondary failure rate. Low-dose combination therapy might be associated with fewer side effects than higher-dose monotherapy and might achieve similar or better glycemic control.¹

Studies have established the beneficial effects on glycemic control of adding metformin, acarbose, and troglitazone to sulfonylurea therapy. A study has also demonstrated that glycemic control improves when acarbose is added to metformin therapy.² Another study has demonstrated improved glycemic control using triple oral antidiabetic therapy.³ To date, however, no studies have assessed the efficacy of combining four different classes of oral antidiabetic agents.

This case report demonstrates the efficacy of combining metformin, glyburide, repaglinide (GlucoNorm), and rosiglitazone maleate (Avandia) for a patient monitored for 6 months. A MEDLINE search was conducted from 1992 to 2002 using MeSH headings "combination therapy," "drugs," "metformin," "glyburide," "GlucoNorm," and "Avandia." No relevant clinical studies were found.

Case report

Mr J.H., a 56-year-old man, has diabetes, atrial fibrillation, peripheral vascular disease, and chronic renal insufficiency. He presented with a weight of 137 kg, a waist circumference of 130 cm, and a body mass index of 41. He was taking enalapril maleate (Vasotec) 10 mg bid, digoxin 0.25 mg daily, furosemide (eg, Lasix) 120 mg daily, allopurinol 300 mg daily, glyburide 10 mg bid, metformin 1 g bid, and metolazone (Zaroxolyn) 2.5 mg bid.

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Cet article a fait l'objet d'une évaluation externe.

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His initial fasting blood sugar levels while using the two diabetic drugs ranged from 17.66 mmol/L to 29.39 mmol/L. A total cholesterol test result was 4.45 mmol/L, thyrotropin was normal, and an electrocardiogram revealed atrial fibrillation with a ventricular rate of 76/min.

The patient had been started initially on metformin, glyburide, and enalapril maleate by his previous family physician. My initial plan after taking over his management was to give him insulin, but he was afraid of needles and after mutual agreement opted for intense dietary modification, exercise, and home glucose self-monitoring accompanied by drug therapy.

I referred him to our diabetic education centre and also added repaglinide at a titrated dose of 4 mg tid. Over a 2- to 3-month period, his fasting blood sugar level fluctuated between 10 and 17 mmol/L, and rosiglitazone maleate was added at a dose of 4 mg bid. This led to a fall in his fasting blood sugar level to between 5.67 and 7 mmol/L. During this time, his hemoglobin HbA_{1c} came down to 9% and was steadily improving. With repaglinide added to his regimen, his weight went from 137 kg to 122 kg; the addition of rosiglitazone maleate was associated with a further steady weight reduction to 117 kg. Due to a concern about his kidney function, I opted to monitor his electrolyte levels, creatinine levels, and creatinine clearance. His albumin-creatinine ratio was 53 mg/mmol/L, and an initial creatinine level was 147 µmol/L giving a creatinine clearance of about 63 mL/min.

The upper limit for use of metformin for patients with kidney disease is 1.5 mg/dL or 132.6 µmol/L to avoid lactic acidosis.⁴ This patient's previous family physician started metformin, glyburide, and enalapril maleate therapy long before evidence of chronic renal insufficiency was present.

Due to the patient's microalbuminuria and obesity, I chose to continue with these medications and strictly monitor his creatinine clearance and other relevant clinical parameters.

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As his blood glucose levels improved, so did his creatinine clearance. His creatinine levels returned to normal at 117 µmol/L.

About 4 months into his therapy, the patient developed jaundice and severe itching. I initially suspected the rosiglitazone maleate caused this, but a computed tomography scan revealed obstructive jaundice with carcinoma of the head of the pancreas.

The patient underwent a Whipple operation, and histology revealed a poorly differentiated carcinoma of the head of the pancreas. During his stay in hospital and postoperatively, he continued his oral diabetic regimen: metformin 1 g bid, glyburide 10 mg bid, repaglinide 4 mg tid, and rosiglitazone maleate 4 mg bid. During his investigation for pancreatic cancer and also postoperatively his weight was steady at 115 to 116 kg. Because of the previous decrease in weight and normalization of his creatinine levels, metolazone, furosemide, and allopurinol were stopped.

Mr J.H. continued to do well on the four diabetic drugs and was scheduled to undergo adjuvant chemotherapy and radiation. During his treatment with the oral diabetic agents, he reported no side effects and maintained an ideal weight and good fasting blood sugar levels. He died about 5 weeks after his Whipple's operation.

Discussion

Sulfonylurea medications improve glycemic control by increasing insulin production. Metformin decreases hepatic glucose production and increases peripheral glucose uptake.³ Repaglinide, a new non-sulfonylurea insulin secretagogue, stimulates the release of insulin from pancreatic B cells by closing the adenosine 5-triphosphate (ATP)-dependent potassium channels.⁵ Rosiglitazone maleate, a glitazone, does not increase insulin secretion but rather increases insulin sensitivity.⁴

The goal of combination therapy is to lower blood glucose levels through synergistic pharmacologic effects. Each oral hypoglycemic agent has its own unique metabolic properties, including effects on gluconeogenesis, insulin release, insulin resistance, body weight, and lipid profiles. When considering combination therapy, therefore, current drug therapy and individual patient characteristics must be addressed.⁵

Given the high secondary failure rate of monotherapy in type 2 diabetes (regardless of agent) and the devastating long-term consequences of poor glycemic control, we must consider a more intensive approach to oral drug therapy. Initiating combination

Editor's key points


- This case report describes the use of four oral hypoglycemic medications to control diabetes: glyburide, metformin, repaglinide (GlucoNorm), and rosiglitazone maleate (Avandia).
- Despite complications of mild renal failure, obesity, atrial fibrillation, and a newly diagnosed pancreatic cancer, control of the patient's blood sugar levels improved significantly on the four-drug regimen.

Points de repère du rédacteur

- Cette étude de cas porte sur l'utilisation de quatre hypoglycémisants oraux pour contrôler le diabète: le glyburide, la metformine, la répaglinide (GlucoNorm) et le maléate de rosiglitazone (Avandia).
- Malgré des complications d'insuffisance rénale légère, d'obésité, de fibrillation auriculaire et la découverte récente d'un cas de cancer pancréatique, le contrôle des glycémies s'est amélioré de façon significative avec chacun de ces médicaments.

drug therapy at low doses can minimize the side effects associated with high-dose therapy, yield additive clinical benefits, and possibly even curtail costs of treatment.¹ Use of four oral drugs is probably best reserved for patients who refuse to use insulin or who react badly to insulin.

Conclusion

This case report highlights that using a combination of four oral hypoglycemic drugs appears to have been successful. 

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Competing interests

None declared

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