CASE REPORT

Upfront Combination Therapy for Type 2 Diabetes Mellitus Using Triple Oral-glucose Lowering Drugs: a Case-based Review.

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Abstract

Type 2 Diabetes mellitus (DM) is a complex metabolic condition characterized by persistent hyperglycaemia and other metabolic abnormalities. Untreated, this condition leads to significant morbidity and mortality. The therapeutic aim in this condition is to establish early normoglycaemia to prevent permanent pancreatic beta islet dysfunction and development of irreversible vascular damage. American and Malaysian guidelines recommend upfront initiation of insulin therapy for patients with catabolic symptoms and very severe hyperglycaemia. Unfortunately, the acceptance rate for insulin therapy among newly diagnosed type 2 DM patients is low.

We report the case of a 71-year-old lady with newly diagnosed type 2 DM. Her random and fasting glucose were 17.3 mmol/L and 13.3 mmol/L respectively which did not improve with diet control. She was commenced on a combination of metformin, sitagliptin and empaglifozin. Her fasting and two-hour post-prandial glucose was 7.5mmol/L and 8.3 mmol/L respectively, after 2 weeks of this combination of oral glucose lowering drugs. We review the basic physiology and pharmacological rationale for the combination utilised and other potential non-insulin regimes.

Initiation of oral glucose lowering drug combination is effective in achieving early glycaemic optimisation in patients with very severe hyperglycaemia in the absence of catabolic symptoms and ketosis. The combination we utilised have minimal risk of hypoglycaemia and is ideal for initiation in the out-patient setting.

Keywords: *type 2 diabetes mellitus, severe hyperglycaemia, insulin resistance, beta-islet dysfunction, pharmacological combination, oral glucose lowering drugs.*

Introduction

Type 2 Diabetes mellitus (DM) is a complex metabolic condition characterised by persistent hyperglycaemia accompanied by other metabolic abnormalities. The underlying pathophysiology is multifactorial including peripheral tissue insulin resistance, increased hepatic glucose output, increased adipocyte lipolysis and impaired incretin response. Persistent hyperglycaemia and hypertriglyceridaemia in type 2 DM induces pancreatic beta islet cell apoptosis via free radical gluco-lipotoxicity which will further aggravate this condition.

The prevalence of DM in adults over the age of 30 years in Malaysia is 24.1% (over 90% of these consist of type 2 DM patients) [1] which is significantly higher than the global prevalence estimate which is 9.4% [2]. Untreated, this condition leads to significant mortality and morbidity from cardiovascular diseases and microvascular organ dysfunction (retinopathy, neuropathy and nephropathy). Indeed, 44.2% of patients presenting with acute coronary syndrome [3] and 65% of patients initiating dialysis in Malaysia [4] are patients with established DM.

It's important to establish normoglycaemia as soon as the diagnosis of DM is made to prevent future diabetes associated complications and mortality, also known as the 'legacy effect' of type 2 DM [5]. Achieving early normoglycaemia is challenging for patients with catabolic hyperglycaemia or patients with very severe hyperglycaemia (Table 1). To achieve this, the Malaysian clinical practice guidelines (MCPG) and American Diabetic Association (ADA) guidelines recommend induction insulin therapy to initiate glycaemic control in type 2 DM patients with very severe hyperglycaemia (fasting blood glucose exceeding 13 mmol/L and 16.7 mmol/L respectively) [1][6].

It is well established that patient-related factors cause under-utilization and delays in initiation of insulin therapy in a significant proportion of type 2 DM patients. Some of the patient 'perceived-barriers' include fear of injectables, perceived risk of hypoglycaemia and negative social stigma [7].

An efficacious oral glucose lowering regime with an acceptable adverse effect profile is highly desired as an alternative to insulin therapy to establish normoglycaemia in this challenging patient cohort. We report a case of a type 2 DM patient in which glycaemic control was induced using combination oral glucose lowering drugs with minimal risks of hypoglycaemia.

Case report

A 71-year-old Eurasian lady presented with a 10 month history of intermittent exertional chest pain. She had no diagnosed chronic medical illnesses apart from obesity.

Her chest pain was described as a retrosternal crushing pain without radiation resolving upon rest. She denied other cardio-respiratory related symptoms. Otherwise, her appetite was good and her weight has been stable. She denied osmotic symptoms (polyuria, polydipsia) or any change to her visual acuity.

Her physical examination was generally unremarkable. Her weight was 82.2kg with a height of 1.53 meters (BMI 35.1 kg/m^2). She was clinically euvolaemic with a blood pressure of 150/83 mmHg and a regular pulse of 96/minute. Chest auscultation revealed normal breath sounds and normal heart sounds with no murmurs. Acanthosis nigricans was not identified and peripheral oedema was absent. Neurological examination was unremarkable. Retinal fundoscopy was not performed.

Laboratory evaluation demonstrated a random glucose of 17.3 mmol/L and dyslipidaemia (total cholesterol 6.0 mmol/L, LDL cholesterol 3.8 mmol/L, Non-HDL cholesterol 5.0 mmol/L, HDL cholesterol 1.0 mmol/L, triglycerides 2.7 mmol/L). Otherwise, her full blood count, liver function tests and renal profile (creatinine 60 µmol/L; estimated GFR=90.85 utilising MDRD), uric acid and bone profile were all normal. Urinalysis was negative for protein. Her chest x-

ray was normal. Her resting electrocardiogram revealed flattened t waves in lead III only and was otherwise normal.

She was diagnosed with stable angina, type 2 diabetes mellitus and dyslipidaemia. She was surprised with the diagnosis of type 2 DM and was initially reluctant to commence glucose lowering drugs. She was commenced on once daily aspirin 150mg and bisoprolol 1.25 mg with atorvastatin 20mg nightly. We commenced a trial of strict diet control for 3 weeks. She was relatively compliant to her diet with no refined sugar intake and healthy food portions but was unable to adhere to a restricted lipid intake. By the end of the trial period, she had a capillary fasting glucose of 13.3 mmol/L (utilizing OneTouch®SelectSimple™ glucometer, Switzerland). Following this, she was commenced on a 2 week course of induction therapy with Janumet (sitagliptin 50mg/ metformin 1 g) 1 tablet twice daily and empaglifozin 25mg daily.

The regime was well tolerated and there was no significant increase in weight or peripheral oedema. On the fifth day of therapy, she developed acute suppurative paronychia of her right great toe which was successfully treated with a five day course of oral ciprofloxacin 500mg twice daily. No dose changes were made to her glucose lowering drugs during this period. She did not experience any hypoglycaemic attacks throughout this period.

After two weeks, her fasting and two-hour post-prandial glucose were 7.5 mmol/L and 8.3 mmol/L respectively. Given the good response to induction therapy, we advised her to adhere to diet control and to continue metformin 1 g twice daily monotherapy (maintenance), aspirin, bisoprolol and atorvastatin long-term.

Discussion

We describe a case of type 2 DM with very severe hyperglycaemia, presenting with stable angina who was successfully treated with combination oral glucose lowering drugs without episodes of hypoglycaemia.

In this patient, we utilised 3 oral glucose lowering drugs namely metformin (biguanide), sitagliptin (dipeptidyl peptidase-4: DPP4 inhibitor) and empaglifozin (sodium glucose cotransporter 2: SGLT2 inhibitor). This is a relatively common combination of oral glucose lowering drugs for type 2 DM. However, our case was unique as we utilized this combination as induction therapy rather than part of a sequential intensification therapy which is the traditional approach in treating type 2 DM.

Each of the drugs we used employ different mechanisms of action and synergistically lowers serum glucose. Furthermore, none of these drugs are associated with a significant risk of hypoglycaemia. It makes this combination regime ideal for intensive induction therapy in the out-patient setting. Table 2 compares pharmacological characteristics between common drugs used in type 2 DM. The top 3 rows are the classes of drugs used by this patient.

The regime we employed addresses multiple target organs involved in type 2 DM namely the liver, kidneys and pancreas. Metformin predominantly acts in the liver to reduce hepatic glucose output via inhibition of gluconeogenesis and increasing hepatic insulin sensitivity [8]. Empaglifozin predominantly acts in the renal proximal convoluted tubule to reduce tubular glucose reabsorption, further reducing hyperglycaemia. Treatment with SGLT2 inhibitors are associated with hyperglucagonaemia [9]. The resultant hyperglucagonaemia is compensated via introduction of sitagliptin, a DPP4-inhibitor. DPP4-inhibitors reduce pancreatic alpha cell glucagon secretion and simultaneously increases pancreatic beta islet secretion of insulin through the enhanced 'incretin effect'.

Further intensification to our regime could potentially include substituting sitagliptin with a GLP1 (glucagon-like peptide-1) - receptor agonist. GLP-1 receptor agonists confer greater amplification of the incretin effect compared to

DPP4 inhibitors and extends an additional benefit of significant weight loss, which is desirable in our patient. However, GLP-1 receptor agonists are currently only available in the injectable form. Other strategies could include addition of alpha-glucosidase inhibitors (AGI) to reduce intestinal glucose absorption and increasing skeletal muscle insulin sensitivity by adding a thiazolidinedione. However, there is variable patient compliance to AGI therapy and a decreasing trend of thiazolidinedione prescription attributed to their adverse effect profile (Table 2).

The majority of type 2 DM patients have asymptomatic disease progressing from pre-diabetes to frank type 2 DM over several years, often presenting to clinicians due to complications of DM. Due to the delay in diagnosis, attempts to achieve early normoglycaemia should be intensively pursued to salvage residual pancreatic beta islet function and to achieve the 'legacy effect'.

I. Pancreatic beta-islet cell function salvage:

States of reversible severe beta cell dysfunction has been increasingly recognized where traditional oral glucose lowering drugs will be rendered ineffective. These occur in type 2 DM patients with very severe hyperglycaemia, symptomatic/catabolic hyperglycaemia and ketosis prone DM. There is clear experimental and clinical evidence that achieving early normoglycaemia or the concept of 'beta-cell rest' can improve pancreatic beta-cell function and first-phase insulin secretion [10]. Once normoglycaemia is achieved, most patients regain their beta islet function and can be managed with dietry restriction alone or combined with oral glucose lowering drugs. The MCPG and ADA guidelines recommend initial insulin therapy for symptomatic hyperglycaemia and very severe hyperglycaemia whilst the National Institute for Health and Care Excellence (NICE) guidelines recommends initial insulin therapy only for symptomatic hyperglycaemia [11]. Additionally, the NICE guidelines recommends oral sulfonylureas as an alternative to insulin therapy for such patients if insulin treatment is declined, provided there is no ketosis.

II. The legacy effect:

Apart from functional beta-islet salvage, observations from post-trial longitudinal studies reveal that patients undergoing early intensive therapy to achieve normoglycaemia experience a continued risk reduction from microvascular disease and to a lesser extent, macrovascular complications. These findings have led to the term 'legacy effect in type 2 DM' being coined [12]. This benefit has been corroborated by multiple post-trial follow-up studies. The shorter the duration of DM prior to intensive therapy, the greater the benefit gained [13]. This benefit is most likely achieved by preventing permanent vascular disease development which would lead to sustained organ dysfunction.

With the available clinical evidence, early intensive therapy appears to have a disease-modifying effect. More research comparing the traditional step-wise escalation therapy and early intensive 'disease modifying therapy' may help optimise management guidelines and may invoke a therapeutic paradigm shift in the future.

Conclusion

A combination regime of oral glucose lowering drugs (biguanide, SGLT2-inhibitor and DPP4-inhibitor) was effective as an induction therapy to achieve normoglycaemia in type 2 DM patients with very severe hyperglycaemia. It may be suitable alternative to insulin in patients without catabolic symptoms or ketosis. It has a low risk of hypoglycaemia and is ideal for therapy initiation in the out-patient setting. More studies are required to assess whether this effect is consistent throughout different patient populations.

Table 1. Hyperglycaemia severity grading adapted from the Malaysian clinical practice guidelines [1].

Severity grade	Fasting blood glucose (mmol/L)	HbA1c (%)
Mild	6 – 7.9	6.5 - 7.4
Moderate	8 – 9.9	7.5 – 8.4
Severe	10 – 13	8.5 - 10
Very severe	>13	> 10

Table2. Pharmacological characteristics of common drugs classes used in type 2 diabetes mellitus

Drug class	Mechanism of action	HbA1c reduction efficacy (%)	Hypoglycaemia	Weight changes	Post-prandial glucose control	CV benefits	Adverse effects (main)
Oral glucose lowering drugs							
Biguanide	Reduce hepatic glucose output	1 - 1.5	No	Neutral	No	Yes	Nausea/ diarrhoea
DPP4 inhibitors	Increases incretin bioavailability	0.5 – 0.8	No	Neutral	Yes	Neutral	Well tolerated
SGLT2 inhibitors	Reduces renal tubular glucose reabsorbtion	0.2 – 0.8	No	Loss	Yes	Yes	Increased genitourinary infection
Sulfonyureas	Insulin secretagogue	0.4 – 1.6	Yes	Gain	No	Neutral	↓glucose, weight gain
Meglitinides	Insulin secretagogue	1 – 1.2	Yes	Gain	Yes	Neutral	↓glucose, weight gain
AG inhibitors	Inhibits luminal sugar breakdown and absorbtion	0.5 – 0.8	No	Neutral	Yes	Neutral	Flatulence, bloating
TZD	Reduces insulin resistance	0.5 – 1.4	No	Gain	No	Yes (pioglitazone)	Heart failure, osteoporosis
Injectable agents							
GLP-1 RA	Enhance incretin effect	0.5 – 1.5	No	Loss	Yes	Yes (liraglutide)	Nausea, anorexia
Insulin	Increased peripheral tissue glucose uptake, antagonize glucagon, anabolism	>2	Yes	Gain	Yes (short-acting analogues)	Neutral	↓glucose, weight gain

Abbreviations: CV (cardiovascular) DPP4 (dipeptidyl-peptidase-4) SGLT2 (sodium glucose cotransporter 2) AG (alpha-glucosidase) TZD (thiazolidinedione) GLP-1 RA (glucagon-like peptide-1 receptor agonist)

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