



THE SAFETY OF TRIPLE THERAPY WITH ORAL ANTIDIABETICS VERSUS INSULIN IN TYPE 2 DIABETES

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ABSTRACT

Purpose: The objective of this study is to compare the safety of insulin versus triple therapy with oral antidiabetics in type 2 diabetes. **Methods:** Observational prospective study was carried out in Dr Sardjito Hospital, Indonesia from May 2007 to September 2008. The target population is patients with diagnosed type 2 diabetes who are failing with oral antidiabetic medication and visits to the diabetes clinic. For each patient data were collected at first visit and three monthly clinic visits on the doses of all drugs used, the physical examination, and laboratory evaluation through medical records. Safety parameter include general physical examination, clinical laboratory evaluation, adverse drug reaction, reporting of adverse event and hypoglycaemic episode. **Result:** One hundred and fifteen patients, 58 men and 57 women, aged 62.35±8.88, diabetes duration of 12.53±6.97 years were studied. There was one patient in either treatment group who experienced major hypoglycaemic episodes. Minor hypoglycaemic episodes occurred in 34.85% of the patients in insulin groups and 26.53% in three oral drugs group. The most frequent adverse event in both groups was gastrointestinal disturbance (28.57% of insulin vs 61.11% of oral triple therapy group). Adverse events occurring in both group included flatulence, abdominal discomfort, diarrhea, and nausea. The insulin group had 59.09% incidence of drug interactions as compared with 69.39% in oral triple therapy groups. **Conclusion:** A patient treated with three oral drugs is subjected to an additive risk of adverse events and drug interaction compared with insulin therapy.

Key words: Safety, insulin, oral antidiabetics, type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus is a multifactor metabolic disease characterized by abnormalities at multiple organ sites. Research in the previous decade has demonstrated the benefit of improved blood glucose control in the prevention of diabetes complications¹. The macrovascular and microvascular complications associated with diabetes mellitus are well documented by the U.K. Prospective Diabetes Study (UKPDS) and other studies, and current management guidelines have suggested more aggressive goals for glycaemic control².

Most patients begin treatment with diet and exercise or incorporate them into their treatment regimen but, unfortunately most patients are unsuccessful in controlling type 2 diabetes through lifestyle modification alone and require antidiabetic agents³. Oral antidiabetic agents are usually prescribed as initial therapy. Although many patients initially attain control, over the long term, there is generally a requirement for intensified and multidrug regimens, ultimately, oral agents alone cannot maintain glycaemic control in many individuals and therapy must be added by the addition of insulin⁴. However, when adding second and third hyperglycaemic medications, the synergy of combinations and other interactions should be considered⁵. A combination of three oral antidiabetic agents for lowering blood glucose should be considered only when patients are already close to target and when circumstances make it difficult to use insulin. The combination of three oral antidiabetic agents is more expensive than using insulin plus metformin, and no benefit has been shown⁶. For patients with poorly controlled glycaemia, the additive risk of adverse events and higher cost of a third oral agent may not be justified unless the target HbA_{1c} is achieved⁷. Multiple medications not only add to the cost and complexity of therapeutic regimens, but also place patients at greater risk for adverse drug reactions and drug-drug interactions. Studies evaluating appropriate prescribing in the elderly consistently find frequent polypharmacy and use of excessive drugs⁸. Recent studies have demonstrated the efficacy of basal insulin as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled with antidiabetic oral agents.

The decision to initiate insulin therapy ultimately belongs to the patient with type 2 diabetes. Common barriers among patients include beliefs and negative stigma that insulin is a personal failure, that insulin is not effective, that insulin causes complications or even

death, or that insulin injections are painful, as well as fear of hypoglycaemia, loss of independence, weight gain, and cost⁹. Therefore this study is conducted with the aim to compare the safety of two possible approaches for managing failure of combination therapy with oral medication : 1) switching treatment to insulin or 2) combination therapy with oral medication (sulfonylurea, metformin, and acarbose) for patient who reluctance to initiate insulin, who experience adverse events, contraindication, and drug-drug interaction.

METHOD

A prospective observational study was carried out in the Dr Sardjito Hospital, Yogyakarta, Indonesia from May 2007 to September 2008. The main objective were to compare the safety of triple therapy with sulfonylurea, metformin, and acarbose versus insulin. The target population is patients with diagnosed type 2 diabetes mellitus who are failing with oral antidiabetic medication and visits the diabetes outpatient clinic of the department of Endocrinology Dr Sardjito Hospital Yogyakarta, Indonesia. The inclusion criteria were subjects 18 years of age or older, a diagnosis of type 2 diabetes, failing with oral antidiabetics and agree to give consent. Subjects were excluded for any of the following reasons : evidence of renal disease (elevated creatinine > 1.4 mg/dl) or a liver disease (alanin aminotransferase > 2.5 times the upper limit of normal).

For each patient, data was collected at first visit and three monthly clinic visits. The data include doses of all drugs used, the physical examination, and laboratory evaluation through medical records. Adverse events and reports of hypoglycaemic episodes were recorded at all study visits. Minor hypoglycaemic episodes define as blood glucose values of < 56 mg/dl (3.1 mmol/l) with or without symptoms that were self-treated. Major hypoglycaemic is an episode with neurological symptoms consistent with hypoglycaemia that require assistance. Fasting plasma glucose, post-prandial plasma glucose, A_{1c} (baseline, month 3, and 6), vital sign and weight monitor at each visit. The primary end point is the reduction in HbA_{1c} values from baseline to the end of the study. The safety parameter included adverse drug reactions, contraindication, and drug-drug interaction.

RESULT AND DISCUSSION

Fourty nine patients on triple oral drugs (22 men and 27 women), aged 62.84±7.85 years, and diabetes duration of 11.92±6.09 years

were studied. The initial A_{1c} levels was 8.08±1.89% which increased to 8.73±2.37% (p=0.041), 6 month later. We compared to insulin groups with similar baseline characteristics. There were sixty six patients, 36 men and 30 women, aged 61.98±9.61 years, and diabetes duration of 12.98±7.57 years. Their baseline A_{1c} level was 8.85±2.02% which decreased to 8.33±1.94% (p=0.011), 6 month later.

Adverse Events

Hypoglycaemic episodes have a major negative impact on the quality of life and safety of people with diabetes mellitus⁷. Many treatments frequently involve augmenting insulin effects directly (injected insulin) or indirectly (increasing insulin release from the pancreatic β-cell, increasing insulin sensitivity, or inhibiting hepatic glucose production). When endogenous insulin levels are increased, hypoglycaemia is always a potential side effect to therapy, and in fact, is one of the most common adverse drug reactions in diabetes¹⁰.

A total of 14 of 49 patients (28.57%) in triple oral therapy and 24 of 66 patients (36.36%) in the insulin group reported hypoglycaemia events. Major events (assistance required) occurred only once in both treatment groups. Minor episodes (symptoms with confirmed blood glucose < 56 mg/dL, no assistance required) was once in both treatment groups (1 episode of 14 in triple oral therapy and 1 of 24 episodes in the insulin group). There were 12 events (24.49%) associated with symptoms only (without confirmed blood glucose reading) for triple oral therapy and 22 events (33.33%) in the insulin group. There was no correlation between the number of subjects reporting hypoglycemic episodes and month-6 A_{1c} values for both treatment groups. Yale (2005) reported that patients with insulin therapy is associated with the highest frequency of hypoglycaemia (16 to 34%)¹¹. In every patient taking insulin the blood glucose level shows peaks and troughs, which can be most clearly shown by home measurements of blood glucose. Since the lowest blood glucose concentrations occur at different times in each patient, it is a great advantage if individual patients know when their own troughs are likely to occur. The commonest times are before lunch and during the night¹².

The other side effects of insulin were red itchy and fatty lumps at injection sites. Red itchy marks and fatty lumps at injection sites occurred in 4 patients and 5 patients, respectively. Their cause is not known but they sometimes develop if injections are repeatedly given over a very limited area of skin. For this reason, it is best to vary the site from day to day¹².

Patient treated for hypoglycaemia may experience drops in glucose levels because of increased physical activity, decreased appetite, incorrect administration of insulin or oral antidiabetic drugs, drug-drug interactions or other causes. Advanced age is a significantly increased risk for hypoglycaemia. One study demonstrated that older nondiabetic subjects had impaired insulin clearance and reduced glucagons, endogenous glucose production and epinephrine response to hypoglycaemia as compared to younger non diabetic subjects¹³.

Many pharmaceutical agents possess side effects that could result in serious morbidity if administered to unsuitable patients. The incidence of gastrointestinal disturbance (flatulence, nausea, diarrhea, and abdominal pain) associated with metformin was lower for the insulin groups (7.58%) than for the triple oral drugs (34.69%). Sheehan (2003) reported that the main side effect of metformin is gastrointestinal disturbance (nausea, abdominal pain, diarrhea) which occurs in approximately 30% of patients. This problem is related to total dose and the rapidity with which the medication is titrated upward. Much of this difficulty can be avoided by administration with food and by increasing the dose by 500 mg per day, every 1 to 2 weeks (thus allowing 3 to 7 weeks before a full dose is reached)¹⁴.

The primary side effect of α-glucosidase inhibitor is flatulence and other gastrointestinal symptoms. Impaired absorption of carbohydrate leads to increased arrival of carbohydrate in the colon, which can cause gas production, diarrhea, and abdominal pain¹⁰. There were 67.35% of patients in triple oral drugs group and

18.18% of patients in the insulin group who experienced side effects. Abdominal discomfort occurred in 16.33% of the patients of the triple oral therapy group compared with 4.55% of the patients in the insulin group. The most frequent adverse event in both groups was flatulence (46.94% of triple oral group vs. 13.64% of the insulin group). Diarrhea occurred in 4.08% of the patients of the triple oral therapy group. Hanefeld et al., (2004) reported that the most common complaint associated with acarbose were gastrointestinal side-effects such as flatulence, diarrhea and abdominal pain. The frequency of any adverse events varied from country to country, for example 52.7% for acarbose and 29.2% for placebo in the German Study and 73.2% and 39% respectively, in a large Canadian trial¹⁵.

Contraindication

There were 3 patients (6.12%) with renal insufficiency taking sulfonylurea, metformin, and acarbose. Metformin is contraindicated in renal failure because of the associated risk for lactic acidosis. It is a rare side effect, occurring particularly in the presence of renal failure, hepatic dysfunction, or tissue ischemia. It can be used at low dosages up to a creatinine clearance of 30 to 60 ml/min and should be avoided with clearances ~30 ml/min. The risk of lactic acidosis due to metformin is negligible in these patients and is unrelated to the plasma concentration of metformin. Indeed, the nearabsence of any cases of lactic acidosis in large observational studies and the fact that metformin levels do not correlate with lactate levels in individuals who do develop lactic acidosis supports the viewpoint that metformin may be "an innocent bystander" in sick patients rather than a causal agent¹⁶. The sulfonylureas have increased potency as the renal function decreases and are contraindicated in severe renal failure. Alfa-glucosidase inhibitors (acarbose) are contraindicated in renal failure. In chronic renal failure, the oral agents that can be used therefore include the insulin secretagogues repaglinide and nateglinide and the thiazolidinediones (rosiglitazone and pioglitazone) with caution. Insulin also can be used safely in renal failure¹¹.

Biguanides can be effective therapy in patients with diabetes, but these medications can be contraindicated because of renal insufficiency, liver disease, or congestive heart failure, or they may not be tolerated because of gastrointestinal side effects¹⁷. In this study, we found that 3 patients with congestive heart failure taking metformin. Tahrani (2007) reported that treatment with metformin is not absolutely contraindicated in patients who have isolated heart failure, and it may be beneficial. Metformin provides a greater degree of cardiovascular protection than would be expected from its antihyperglycaemic actions alone and is the first drug of choice for the treatment of type 2 diabetes. The decision to stop or continue metformin in the presence of heart failure should be individualised to the particular patient until further evidence is available.

Drug-Drug Interaction

Polypharmacy is common among the elderly, because of the desire to simultaneously manage glycaemia, hyperlipidaemia, hypertension, and other associated conditions. Yet, polypharmacy can affect cognitive ability, physical functioning, and depression through drug-drug or drug-disease interactions¹⁸. Several adverse drug interactions between oral antidiabetics and other commonly prescribed medications are recognized that increase the risk of hypoglycaemia. The study showed that the insulin group had 53 incidences of drug interactions (in 39 patients) as compared with 60 incidences (in 34 patients) in triple oral therapy groups (Table 1). A total of 9 of 14 patients (64.28%) in triple oral therapy and 14 of 24 patients (58.30%) in the insulin group that experienced hypoglycaemia, associated with drug-drug interaction.

It is likely that many elderly patients have other concurrent illnesses and thus could be taking medications that interfere with or prolong the action of their diabetes medications. Optimization of insulin or oral agent therapy to the patient's lifestyle can help decrease the incidence of hypoglycaemia. Frequent glucose monitoring is also important, especially in patients who are hypoglycaemia unaware.

CONCLUSION

Table 1: Drug-drug Interactions

Drugs	Effect	Group (n episodes)	
		Insulin	Triple oral drugs
Fibric acid derivatives	Increased effect	3	3
Allopurinol	Increased effect	0	1
NSAID, low dose aspirin	Increased effect	12	22
Cyclic antidepressant	Increased effect	12	12
Beta-blockers	Increased effect	3	4
Diuretics	Increased effect	9	7
Calcium channel blocking drugs	Increased effect	14	11

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REFERENCES

1. Kimmel B, Inzucchi SE. Oral Agents for Type 2 Diabetes : An Update. *Clinical Diabetes* 2005; (23):2
2. Cook MN, Girman GJ, Stein PP, Alexander CM, Holman RR. Glycemic Control Continuous to Deteriorate After Sulphonylurea are Added to Metformin Among Patients With Type 2 Diabetes. *Diabetes Care* 2005; (28):5
3. Fowler MJ. Diabetes Treatment, Part 2 : Oral Agents for Glycemic Management. *Clinical diabetes* 2007; (25):4
4. Kuritzky L. Addition of Basal Insulin to Oral Antidiabetic Agents : A Goal Directed Approach to Type 2 Diabetes Therapy. *MedGenMed* 2006; 8(4):34
5. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B. Management of Hyperglycemia in Type 2 Diabetes : A Consensus Algorithm for The Initial and Adjustment of Therapy. *Diabetes Care* 2006;(12)8

6. Heine RJ, Diamant M, Mbanja JC, Nathan DM. Diabetes Mellitus Management of Hyperglycemia in Type 2 Diabetes. *BMJ* 2006; 333
7. Rosenstock J, Banarer S, Owens D. Insulin Strategies in Type 1 and Type 2 Diabetes Mellitus. in Fonseca VA, *Clinical Diabetes, Translating Research into Practice*. Saunders, Philadelphia 2006
8. Good CB. Polipharmacy in Elderly Patients with Diabetes. *Diabetes Spectrum* 2002; (15):4
9. Funnel MM. Quality of Life and Insulin Therapy in Type 2 Diabetes mellitus. *Insulin. Excerpta Medica* 2008:31-36
10. Fowler MJ. Hypoglycemia, *Clinical Diabetes* 2008; 26(4)
11. Yale JF. Oral Antihyperglycemic Agents and Renal Disease : New Agents, New Concepts. *J Am Soc Nephrol* 2005;16:S7-S10
12. Watkins PJ. ABC of Diabetes. 5th Edition, BMJ Publishing Group, London 2003: 32-36
13. Guy DA, Sandoval DA, Davis SN. Hypoglycemia in Diabetes. In Fonseca VA, *Clinical Diabetes. Translating Research into Practice*. Saunders, Philadelphia 2006.
14. Sheehan MT. Current Therapeutic Options in Type 2 Diabetes Mellitus : A Practical Approach. *Clinical Medicine & Research* 2003;(1)3:189-200
15. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Pupp M. Acarbose Reduce The Risk for Myocardial Infarction in Type 2 Diabetic Patients : Meta Analysis of Seven Long-term Studies. *European Heart Journal* 2004;25:10-16
16. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved Clinical Outcomes Associated with Metformin in Patients with Diabetes and Heart Failure. *Diabetes care* 2005; 28:2345-2351
17. Meneilly GS, Ryan EA, Radziuk J, Lau DC, Yale JF, Morais J, Chiasson JL, Lhoref RR, Mheux P, Tessier D, Wolever T, Jose RG, Elahi D. Effect of Acarbose on Insulin Sensitivity in Elderly Patients with Diabetes. *Diabetes Care* 2000; 23:1162-1167
18. Gregg EW, Brown A. Cognitive and Physical Disabilities and Aging-related Complication of Diabetes. *Clinical Diabetes* 2003;21(3)