Effects of Gliclazide and Insulin Therapy on Thromboxane B₂ and 6-Keta-PGF₁α Levels in Type II Diabetic Patients

Abstract: Diabetic patients show hemobiological abnormalities such as increased platelet adhesiveness, platelet hyperaggregability, decreased platelet half life, hemorheological abnormalities and altered fibrinolysis, perhaps contributing to a procoagulative state. Gliclazide, a novel sulfonylurea in routine clinical use, was thought to have effects on prostanoid release and platelet function. We studied thromboxane A₂ metabolite; serum thromboxane B₂ (TXB₂) and the prostacyclin metabolite, 6-keto-PGF₁α to assess the efficacy of gliclazide on these parameters. Two groups of age and sex matched type II diabetics were examined in the study. There were 16 subjects in each group (F:M= 10/6). The study period was 12 weeks. Gliclazide was given to the first group and insulin to the second. Following parameters were evaluated to see the effect of good control. HbA₁c, cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, serum TXB₂, 6-keto-PGF₁α levels were measured before and after 3 months of therapy. There was no significant change in TXB₂ (2.24±0.2 to 2.08±0.4 nmol/L) and 6-keto-PGF₁α (2.53±0.2 to 2.15±0.1 nmol/L) levels in patients treated with insulin despite the amelioration in the HbA₁c levels. Therapy with gliclazide was followed by a significant decrease in both serum TXB₂ levels (4.18±0.7 to 2.72±0.4, p=0.039) and 6-keto-PGF₁α (2.97±0.3 to 2.03±0.1, p=0.0047). TXB₂/6-keto-PGF₁α ratio did not change both after insulin (1.09±0.5 to 1.06±0.8) and gliclazide (1.31±0.9 to 1.32±0.4) treatment.

According to the data in our study, gliclazide therapy decreased TXB₂ levels as well as 6-keto-PGF₁α levels so that ratio of TXB₂/6-keto-PGF₁α did not change, which would mean that gliclazide has neutral effect on diabetic microvascular complications.

Key Words: Non insulin dependent diabetes, gliclazide, thromboxane B₂, 6-keto-PGF₁α.
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smooth muscles, the decrease in PG\(_{I_2}\) levels and the increase in TXA\(_2\) levels in diabetes could facilitate the development of microthrombi, leading to diabetic microvascular complications.

Gliclazide is a second generation sulfonylurea that is widely used in the treatment of NIDDM. In addition to its metabolic effects, there are some reports implicate that gliclazide has beneficial effects on the haemobiological abnormalities of NIDDM, although one report showed no effect (6). In our previous study to investigate the effect of good glycemic control on platelet function, we measured changes in plasma beta thromboglobulin and platelet factor 4 (PF4) levels and platelet aggregation after 3 months of treatment with insulin and gliclazide. We could not demonstrate significant change in platelet functions although there was a significant reduction in HbA1c levels (7). With regard to platelet functions, several groups have demonstrated a significant reduction in serum and intraplatelet beta thromboglobulin and TX \(_B_2\). Animal studies have shown a correction of the TXA\(_2\)/PG\(_I_2\) imbalance, by this drug (8, 9).

Platelet dysfunction, platelet-endothelium interactions in the early stages of diabetes cause microvascular damage and tendency to atherosclerosis. Risk of microangiopathy can be reduced by optimising PG\(_{I_2}\) and TXA\(_2\) levels which are the markers of platelet-endothelium inter reaction. The aim of this study is: - to emphasise the known effects of gliclazide on TXB\(_2\) and 6-keto-PGF\(_{1\alpha}\) - to see whether the direct effect of gliclazide on these parameters is different from the metabolic control of diabetes. We switched to insulin treatment in a group of patients who had poor diabetic control, to detect if the normalisation of TXB\(_2\) and 6-keto-PGF\(_{1\alpha}\) is due to good diabetic control.

Materials and Methods

Patients

Sixteen patients whom were not achieved good metabolic control with gliclazide therapy in 3 months, were selected for gliclazide treatment group (group I) and 16 NIDDM patients whom were achieved good metabolic control with insulin were selected for insulin treatment group (group II). Details about patients were given in table 1.

In group I, all patients were switched to gliclazide for 3 months. Patients were administered maximum 160 mg/day gliclazide.

In group II, all patients switched to insulin from oral...
antidiabetics other than gliclazide for 3 months.

Diabetic patients were identified using the following exclusion criteria: Type I diabetics, patients treated with prostaglandin synthesis inhibitors, adrenocorticooids, salicylates, dipyridamole, theophylline, Vitamin E and antilipemic drugs and patients had good metabolic control after gliclazide treatment.

Diabetic neuropathy was examined by electrophysical examination, retinopathy was assessed by ophthalmoscopic examination and coronary heart disease was examined by anamnesis and ECG.

Method

Assessment of the patients were performed at the baseline and after completion of three months of therapy. These included detailed medical history, clinical examination, and determination of fasting plasma glucose (glucose oxidase method), HbA1c (colorimetric method), serum triglycerides (enzymatic colorimetric method GPO-PAP), total cholesterol (enzymatic colorimetric method CHOD-PAP), HDL cholesterol (Tungstophosphoric acid hydrate-magnesium chloride precipitation method), LDL cholesterol (by Friedewald formula), TXB₂ and 6 keto PGF₁α levels (by RIA). We collected the blood for TXB₂ and 6-keto PGF₁α, in a tube with EDTA, centrifuged immediately and froze the plasma rapidly. If blood samples could not be processed rapidly, indomethacin or aspirin was added to the anticoagulant as recommended.

Results are given as medians and ranges are presented as mean±SD. Statistical analyses were performed by using standard t test.

Results

HbA1c values decreased significantly in group I, but there was no change in gliclazide group because these patients were selected from the subjects that metabolic control could not be achieved. Fasting plasma glucose levels were decreased significantly in group I, but not in group II. Cholesterol, triglycerides, HDL and LDL cholesterol levels did not change in both groups (table 2).

Three months of gliclazide therapy resulted in a significant decline in serum TXB₂ and 6-keto-PGF₁α levels. In spite of significant decrease in HbA1c levels, neither TXB₂ nor 6-keto-PGF₁α levels changed after insulin treatment. TXB₂/6-keto-PGF₁α ratio did not change both after gliclazide and insulin treatment (table 3).

Discussion

Abnormalities of arachidonic acid metabolism and of the prostaglandine pathway have been studied following the development of techniques for the assay of thromboxane A₂ and thromboxane B₂. An increase in TXA₂ levels during diabetes has been clearly shown (10, 11). This abnormality is confirmed by assay of its stable metabolite TXB₂ (12, 13). Furthermore PGl₂-platelet interaction is impaired during diabetes because of reduced sensitivity of platelets to prostacyclin (14, 15, 16). TXA₂ and PGl₂ acts on platelets by influencing the activity of adenylate cyclase. The opposing effects of TXA₂ and prostacyclin on adenylate cyclase have fostered the theory that platelet homeostasis is dependent on a reciprocal regulation of cyclin AMP levels by PGl₂ and TXA₂ (17).

As PGl₂ inhibits platelet aggregation and relaxes vascular smooth muscles the decrease in PGl₂ levels and the increase in TXA₂ levels in diabetes could facilitate the development of microthrombi, leading to diabetic microvascular complications. One study was demonstrated that TXB₂/6 keto-PGF₁α ratio was decreased from 4.6 to 1.6 by gliclazide treatment (18).

In diabetics ▲5, ▲6 desaturase activity is reduced, causing a subsidence in arachidonic acid production and its metabolite PGl₂ synthesis (1, 19). Furthermore lipid
phospholipids (8, 18) some others believe that it does not affect TXA₂ synthesis (6).

In vivo and in vitro radical scavenger effect of gliclazide inhibits lipid peroxidation, causing an increase in PG₁₂ synthesis (20). According to the data in our study, gliclazide therapy decreased TXA₂ levels as well as PG₁₂ levels. Therefore the same TXA₂/PG₁₂ ratio obtained at the end of the study would mean that gliclazide has neutral effect on diabetic microvascular complications. Decrease of TXA₂ levels found in our study is compatible to the results of other investigators (8, 18). Decrease in PG₁₂ levels can be explained as follows:
- The time period for gliclazide therapy might not be sufficient to overcome the oxidative stress in endothelium and to start PG₁₂ synthesis
- Gliclazide might reduce PG₁₂ synthesis by inhibiting the secretion of arachidonic acid from endothelium as well as inhibiting its secretion from platelets.

References


