Picotamide, a Dual TXB Synthetase Inhibitor and TXB Receptor Antagonist, Reduces Exercise-Induced Albuminuria in Microalbuminuric Patients With NIDDM

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We investigated the short-term effect of the TXB inhibitor picotamide on albuminuria induced by exercise in 15 microalbuminuric (i.e., with UAE at rest between 20 and 200 μg/min) type II diabetic patients (12 men and 3 women, age 56 ± 2, BMI 28 ± 1 kg/m^2) and in six normal age-matched control subjects. The diabetic subjects performed five submaximal exercise tests (90% of theoretical heart rate) on a cycle ergometer: the first two under basal conditions; the third and fifth after subjects had received picotamide (900 mg/day) or placebo (3 tablets/day) for 10 days; the fourth exercise always was performed after 10 days of wash-out. Control subjects performed two exercises: the first in baseline conditions and the second after 10 days of picotamide administration (900 mg/day). When diabetic patients were untreated, a significant ($P < 0.05$) increase in UAE with respect to baseline levels was observed immediately after and 1 h after the exercise test. After picotamide administration, UAE significantly decreased ($P < 0.05$) immediately after and 1 h after exercise, as compared with diabetic patients given a placebo. In normal subjects, exercise was followed by a slight increase in UAE, which was not significantly affected by picotamide administration. Our results show that short-term administration of picotamide is associated with a reduction in UAE after exercise in type II diabetes patients with microalbuminuria while at rest. Picotamide, a TXB synthetase and receptor inhibitor, may decrease exercise-induced albuminuria in diabetic patients through a reduction in circulating TXB levels and inhibition of TXB action, which in turn may act by lowering glomerular capillary hydraulic pressure.
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Diabetic nephropathy, one of the main consequences of diabetic angiopathy, is known to increase morbidity and mortality in diabetic patients (1,2). Before the onset of overt diabetic nephropathy, diabetic patients experience a silent period of variable duration during which they have only microalbuminuria: UAE of 0.03–0.3 g/day (20–200 μg/min) (3).

Some have suggested that platelet activation contributes to the pathogenesis of both the macrovascular and microvascular complications of diabetes mellitus (4–9). Evidence linking platelet activation with diabetic nephropathy comes from a study showing that the specific inhibitor of TXB synthetase UK-38,485 significantly reduces microalbuminuria in diabetic patients at rest, as compared with patients given a placebo (10). Dipyridamole, a commonly used antiplatelet drug (11,12), has been reported to decrease UAE in adults with overt diabetic nephropathy (13–15). Another antiplatelet agent, indomethacin, a cyclo-oxygenase inhibitor, has been shown to have beneficial effects on kidney function in human and experimental diabetes (16–18). Recent experimental evidence suggests that these drugs may reduce proteinuria by causing efferent arteriolar dilatation (19,20).

Picotamide is a drug that has shown platelet-inhibitory effects in vitro and in humans (21,22). Recently, preliminary findings indicate that this drug both inhibits TXB-synthetase and acts as a TXB antagonist at the receptor level in vitro and in vivo (23).

Physical exercise can induce abnormal increases in UAE in diabetic patients with microalbuminuria while at rest (24). Recent studies have shown that short-term inhibition of ACE may reduce exercise-induced microal-

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TXB, thromboxane; type II diabetes, non-insulin-dependent diabetes mellitus; UAE, urinary albumin excretion; BMI, body mass index; type I diabetes, insulin-dependent diabetes mellitus; BP, blood pressure; sBP, systolic blood pressure; ACE, angiotensin converting enzyme; RIA, radioimmunoassay; CV, coefficient of variation; PDGF, platelet derived growth factor.

TABLE 1
Clinical characteristics of the subjects

	Sex (men/women)	Age (yr)	BP (mmHg)	Heart rate (beats/min)	Blood glucose (mM)	BMI (kg/m^2)	HBA_{1c} (%)	Duration of diabetes (mo)
Diabetic	12/3	56 ± 2	134/86 ± 4/2	71 ± 2	8.8 ± 0.7	28 ± 1	7.8 ± 0.2	93 ± 12
Normal	4/2	53 ± 2	149/91 ± 2/2	72 ± 3	4.1 ± 0.3	25 ± 0.3	—	—

Data are means ± SE.

buminuria in normotensive type I and type II diabetic patients (25,26).

Our study investigated the short-term effect of picotamide on albuminuria induced by exercise in type II diabetic patients with microalbuminuria while at rest.

RESEARCH DESIGN AND METHODS

The subjects of our study were 12 male and 3 female type II diabetes patients (age 56 ± 2, BMI 28 ± 1 kg/m^2). They were selected from a population of about 200 type II diabetes patients treated on a regular basis at the outpatient clinic of the Cattedra di Clinica Medica, University of Brescia, Italy. We used the following criteria: 40–65 yr of age, known duration of diabetes >12 mo, HbA_{1c} <10%, stable BMI <35 kg/m^2, supine BP <160/95 mmHg, serum creatinine <106 μmol/L, UAE between 0.03 and 0.3 g/day in samples assessed weekly during the 3 mo before the study, and no cardiovascular, hepatic, or systemic diseases (Table 1). The patients were not taking any drugs other than those for treatment of their diabetes. Owing to the high intraindividual variability of UAE, only patients who had variations within 15% of their average rate, measured by weekly assays in the 3 mo before the study, were included (27).

The patients were treated with diet and oral hypoglycemic agents (5–15 mg/day glyburide or glipizide or 80–160 mg/day gliclazide). For 3 mo before and during the study, the patients followed an isocaloric diet (about 0.13 $mJ \cdot kg^{-1} \cdot day^{-1}$: 50% carbohydrates, 35% lipids, 15% proteins) with no restriction on sodium intake.

The study used six normal control subjects, matched for sex and age with the diabetic patients. Their UAE while at rest was <0.03 g/day in three different 24-h urine samples collected weekly the month before the study (Table 1).

The diabetic patients performed five physical exercise tests, and the control subjects performed two physical exercises. For each test, all the subjects came to the outpatient department at 0800 with a 24-h urine sample collected the previous day for UAE measurement. During the 24-h period of urine collection the subjects were asked to follow the isocaloric diet detailed above and to avoid heavy or unusual physical exercises. A variation in UAE <15% of the subject's average rate was considered a reasonable parameter to validate that subjects followed the dietary and exercise instructions.

Subjects underwent a blood sampling for routine hematochemical tests and then remained recumbent for 1 h and drank 500 ml of water. At 0900 each subject performed an exercise test on a cycle ergometer (25). When heart rate and BP had returned to basal values (after 10 to 20 min), the subject provided a sample of urine for assay of albumin concentration. Each subject again remained recumbent for 1 h and drank 500 ml of water, then provided another urine sample for UAE measurement. Blood glucose concentrations were monitored at rest, at the end of exercise, and 30, 60, and 90 min after the end of exercise. Subjects were asked to collect their urine until 0800 the next day for albumin assay. The same investigator followed up with the same subjects.

The diabetic patients performed the first two physical exercises under basal conditions to evaluate the reproducibility of the duration of exercise and of UAE after exercise. In all patients, the difference in albumin excretion between the first two exercise tests was not >15%.

The patients performed the third exercise test after a 10-day administration of either placebo (3 tablets/day) or picotamide (900 mg/day). After this first treatment period, all the patients underwent a 10-day wash-out, at the end of which they performed the fourth exercise and started the second treatment period with picotamide or placebo according to a cross-over protocol. A randomized double-blind design (Fig. 1) was used to assign the patients to the two different treatment schedules (group 1, picotamide-placebo, $n = 8$; placebo-picotamide, group 2, $n = 7$).

Control subjects performed two cyclo ergometric tests: the first in baseline conditions and the second after 10 days of administration of picotamide (900 mg/day).

We measured albuminuria with commercial RIA kits (Sclavo, Siena, Italy; intraassay CV 5.1%; interassay CV 6.3%; sensitivity limit of the assay 0.1 mg/L), and HbA_{1c} by a chromatographic method (BioRad, Milano, Italy; normal range 3–6%). Plasma glucose was determined by the glucose oxidase method (Beckman Glucose Analyzer II), and serum creatinine with a method based on the Jaffe reaction. All samples from the same patient were assessed together and in duplicate.

Absolute values of exercise-induced UAE were expressed as median values and ranges (in parentheses)

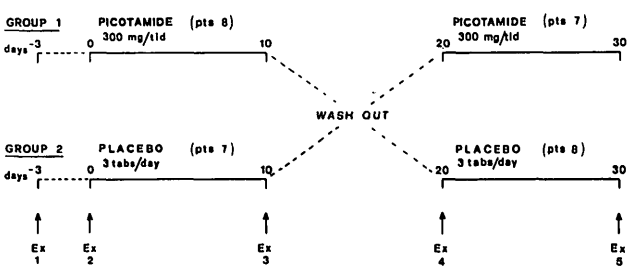

FIG. 1. Study protocol: Randomized, double blind, and crossover.

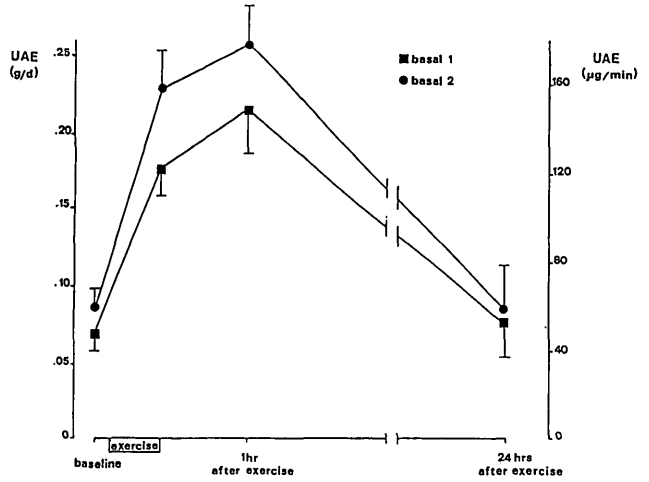

FIG. 2. UAE at rest, at the end of exercise, and 1 and 24 h after exercise. Exercises performed in basal conditions in 15 microalbuminuric type II diabetes patients. Values are mean ± SE. The vertical axes show UAE values expressed either in SI units (left; g/day) or in conventional units (right; μg/min). Conversion: 1 μg/min = 0.00144 g/day.

and analyzed with the nonparametric technique of Wilcoxon, owing to nonhomogenous variances. The results in Figs. 2 and 3 are given as means ± SE for clarity. Correlation between UAE 1 after exercise and exercise-induced increases in sBP, baseline blood glucose, and HbA_{1c} was performed by using linear regression analysis. All the other variables in the study were expressed as means ± SE and were compared with the standard paired or unpaired Student's *t* test. All calculations were performed with the RS/1 package on an IBM PC/AT computer.

RESULTS

Blood glucose did not change significantly during the various exercise tests in both normal and diabetic subjects; no hypoglycemic episodes were observed in diabetic subjects.

When diabetic patients were untreated, no significant differences in baseline UAE were observed between the two exercise tests performed (Fig. 2). At the end of exercise, sBP (mean of the two tests) and UAE (median of the two tests) increased significantly: sBP from 137 ± 2.5 to 188.3 ± 3.1 mmHg ($P < 0.01$) and UAE from 0.05 (0.03–0.16) to 0.12 (0.04–0.51) g/day ($P < 0.001$). UAE 1 h after exercise also increased with respect to baseline levels: median of the two tests was 0.13 (0.03–0.6) g/day ($P < 0.001$).

Normal subjects had a slight ($P < 0.05$) increase in UAE with respect to the baseline level of 0.01 (0.01–0.02) g/day: immediately after exercise UAE was 0.025 (0.02–0.03) g/day; and 1 h after exercise it was 0.02 (0.02–0.035) g/day. UAE and sBP 24 h after exercise were similar to the baseline rate in all the subjects.

Compared with values seen under basal conditions and after the placebo was administered, UAE at rest was slightly, although not significantly, reduced by picotamide. Neither picotamide nor placebo affected BP. Immediately after exercise, UAE was significantly ($P < 0.001$) reduced by picotamide: 0.05 (0.03–0.19) g/day versus the placebo result of 0.13 (0.05–0.35) g/day (Fig. 3).

sBP levels at the end of the exercise after picotamide (187.6 ± 3.7 mmHg) were similar to those observed after placebo (187 ± 3.7 mmHg). UAE 1 h after exercise also was significantly ($P < 0.001$) lower after picotamide: 0.06 (0.04–0.2) g/day versus the placebo result of 0.13 (0.04–0.39) g/day. We confirmed these data by examining separately group 1 and group 2 diabetic patients.

All the diabetic patients performed the fourth exercise test after 10 days of wash-out without therapy. Baseline UAE and UAE measured immediately after and 1 h after exercise were similar to those obtained after placebo administration.

In the control subjects, picotamide did not significantly affect UAE: at rest, UAE was 0.01 (0.01–0.015) g/day; immediately after exercise, it was 0.02 (0.02–0.03) g/day; and 1 h after exercise, it was 0.025 (0.01–0.03 g/day).

In diabetic patients, both after placebo and after picotamide, we observed no significant correlation between UAE 1 h after exercise and either the increase in sBP induced by exercise or baseline blood glucose and HbA_{1c} levels.

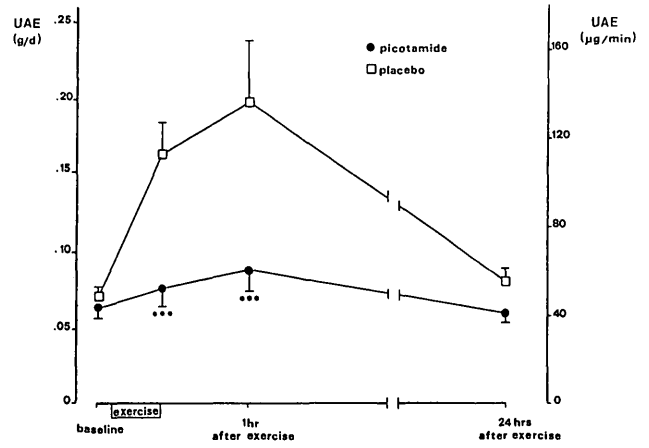

FIG. 3. UAE at rest, at the end of exercise, and 1 and 24 h after exercise after picotamide or placebo in 15 microalbuminuric type II diabetic patients. Values are mean ± SE. The vertical axes show UAE values expressed either in SI units (left; g/day) or in conventional units (right; μg/min). Conversion: 1 μg/min = 0.00144 g/day. *** $P < 0.001$ vs. placebo

DISCUSSION

Our results show that short-term administration of the TXB inhibitor picotamide is associated with a reduction in UAE after exercise in type II diabetes patients with microalbuminuria while at rest and with normal or borderline elevated BP levels.

Albuminuria in diabetic patients might be studied to monitor the progression of the nephropathy and might enable the effects of various drug treatments to be evaluated more effectively (24,26,28,29). Our study confirms that a submaximal exercise test induces typical

large increases in UAE in diabetic patients in the incipient stage of diabetic nephropathy, whereas it causes only marginal changes in UAE in normal subjects. Therefore, even if the precise mechanism responsible for exercise-induced UAE remains to be clarified, our results confirm that this clear-cut phenomenon is a characteristic feature of patients with incipient diabetic nephropathy (24–26).

In these patients, who already have structural changes in the glomerulus, the increase in systemic BP during exercise and the consequent higher intraglomerular filtration pressure may induce increased excretion of albumin (25,26).

Platelet hyperactivity might play a role in the pathogenesis of diabetic nephropathy with an unknown mechanism. Increased PDGF secretion may provide mesangial expansion (30), influence the contractile state of the glomerular mesangium, and neutralize the fixed negative charge of the glomerular filtration barrier (31). Increased platelet generation of TXB also has been observed in multiple models of experimental kidney diseases (32) and might be involved in the pathogenesis of microalbuminuria in diabetic patients (8,10,33). In fact, inhibition of TXB synthetase has been shown to cause a 73% decrease in UAE in microalbuminuric type II diabetic patients at rest (10). Chronic treatment with aspirin and dypiridamole or with dypiridamole alone also has been shown to decrease UAE in diabetic patients with either overt (15) or incipient (34) nephropathy. Finally, indomethacin, a cyclo-oxygenase inhibitor, induces a significant reduction in UAE in patients with incipient diabetic nephropathy (18). The increase in serum TXB levels observed during exercise in diabetic patients has led to the hypothesis that TXB also may play a role in the pathogenesis of exercise-induced UAE in diabetic patients (35).

Picotamide, a new antiplatelet agent derivative of isophtalic acid, inhibits TxA2 synthesis and antagonizes the TxA2 receptor. Clinical use of picotamide could overcome the well-known shortcomings of cyclo-oxygenase inhibitors and pure TxA2 synthetase or receptor antagonists (36–38). TxA2-synthetase inhibition enhances the endogenous synthesis of prostacyclin, whereas TxA2-receptor antagonism prevents accumulated endoperoxides from activating platelets and smooth muscle cells. Picotamide has platelet inhibitory effects in vitro and in humans (21,22). It competitively inhibits human platelet aggregation induced by the stable endoperoxide analogue U46619 and by authentic TxA2 (23). Picotamide also has been suggested to have similar potency in inhibiting either TxA2 synthetase or TxA2 receptor and to exert simultaneously both effects at active concentrations (23).

Our data show that short-term picotamide-mediated inhibition of TXB, and acute (25,26,39) or chronic (40) ACE inhibition, significantly decreases exercise-induced UAE in patients with incipient diabetic nephropathy without substantially affecting either baseline or exercise BP levels. Moreover, picotamide does not affect the slight increase in exercise-induced UAE observed in normal subjects.

Therefore, we conclude that the reduction in TxA2 synthesis and/or inhibition of TxA2 action caused by picotamide may have a specific counteracting effect on the increase in intraglomerular capillary pressure responsible for the abnormal exercise-induced albuminuria in diabetic patients with early stage nephropathy. The finding that short-term TXB inhibition can reduce exercise-induced UAE in diabetic patients with incipient nephropathy suggests that treatment with picotamide could slow the progression of the complication in this early stage.

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