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*Original Citation:*

Picotamide: an inhibitor of the formation and effects of TxA2 / P. A. MODESTI. - In: CARDIOVASCULAR DRUG REVIEWS. - ISSN 0897-5957. - STAMPA. - 13:(1995), pp. 353-364. [10.1111/j.1527-3466.1995.tb00219.x]

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*Published version:*

DOI: 10.1111/j.1527-3466.1995.tb00219.x

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# Picotamide: An Inhibitor of the Formation and Effects of $\text{TxA}_2$

Pietro Amedeo Modesti

*Clinica Medica e Cardiologia, Center for Heart and Thrombosis Research, University of Florence, Florence, Italy*

**Key Words:** Picotamide— $\text{TxA}_2$  antagonists— $\text{TxA}_2$  synthase inhibitors—Peripheral vascular diseases—Renal diseases—Myocardial ischemia—Inflammatory bowel disease.

## INTRODUCTION

After the discovery of thromboxane  $\text{A}_2$  ( $\text{TxA}_2$ ) by Hamberg in 1975 (31), considerable efforts have been made to find a drug therapy to control its biological effects. Platelets produce a considerable amount of  $\text{TxA}_2$  during aggregation and are involved in thromboembolic diseases. Early antithrombotic and anti $\text{TxA}_2$  therapies were viewed as antiplatelet treatments, and the cyclooxygenase inhibitors, particularly aspirin, became the drugs of choice for antithrombotic therapy. The usefulness of these drugs was limited because they do not specifically block  $\text{TxA}_2$ . Thus, a more specific and effective drug to inhibit  $\text{TxA}_2$  was sought. Another compelling reason to develop new specific and effective  $\text{TxA}_2$  inhibitors was the discovery that many cells in addition to platelets, such as monocyte-macrophages, endothelial, and vascular muscle cells (44,55,63), synthesize and release  $\text{TxA}_2$ . Even cells that do not synthesize  $\text{TxA}_2$  at rest may express cyclooxygenase and synthesize  $\text{TxA}_2$  when stimulated by inflammatory cytokines (67). Thus,  $\text{TxA}_2$  may represent an important mediator of different inflammatory processes: it has diverse biological effects, including contraction of vascular and pulmonary smooth muscle, lysis of cell membranes, and promotion of leucocyte adhesion. As a consequence,  $\text{TxA}_2$  may play a role not only in platelet aggregation but also in renal disease, chronic bowel disease and various cardiovascular disorders, including coronary artery disease.

Because of the possible wide-ranging effects of  $\text{TxA}_2$ , the search for effective inhibitors of  $\text{TxA}_2$  has been expanded. These inhibitors are being investigated as part of a general treatment strategy to be used in several diseases where increased  $\text{TxA}_2$  formation plays a pathophysiological role.

Two specific anti $\text{TxA}_2$  approaches were initially proposed: inhibition of  $\text{TxA}_2$  synthase and inhibition of  $\text{TxA}_2$  receptors, but in clinical trials neither approach offered any

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Address correspondence and reprint requests to: Dr. Pietro Amedeo Modesti, Clinica Medica e Cardiologia, Center for Heart and Thrombosis Research, University of Florence, Viale Morgagni 85, 50134 Florence, Italy

advantage (21). Indeed, from a pharmacological point of view, the problems with both of these approaches were evident.  $\text{TXA}_2$  synthase inhibitors lead to accumulation of endoperoxides prostaglandin  $\text{H}_2$ /prostaglandin  $\text{G}_2$  ( $\text{PGH}_2/\text{PGG}_2$ ), which possess the main biological activity of  $\text{TXA}_2$  and share a common receptor with  $\text{TXA}_2$  (68). Antagonists at the  $\text{PGH}_2/\text{TXA}_2$  receptor can be displaced by native  $\text{TXA}_2$  if it is present at sufficiently high concentrations in the vicinity of aggregating platelets or  $\text{TXA}_2$ -forming cells (i.e. at the sites where receptor blockade is mostly required).

A newly developed class of dual  $\text{TXA}_2$  inhibitors, composing drugs that combine  $\text{TXA}_2$  synthase inhibitory activity with  $\text{TXA}_2/\text{PGH}_2$  receptor antagonist activity, seems to represent the ideal solution for effective  $\text{TXA}_2$  blockade. The  $\text{TXA}_2$  synthase inhibitor property may augment the synthesis of vasodilatory prostaglandins at the expense of  $\text{TXA}_2$ , whereas the receptor antagonist activity prevents the accumulating  $\text{PGH}_2$  from stimulating the  $\text{TXA}_2/\text{PGH}_2$  receptor. A balance between these two activities is the most important requirement for dual inhibitors. Picotamide satisfies these requirements.

## CHEMISTRY

Picotamide is a methoxy derivative of the 4-hydroxy-isophthalic acid [N,N'-bis(3-picolyl)-4-methoxy-isophthalamide] (CAS 80503-63-8). Its chemical structure is shown in Fig. 1. Its synthesis and that of some analogs were published initially by Orzalesi *et al.* (49). Picotamide is a white, odorless, crystalline powder that melts at 95–97°C. Its molecular formula is  $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_3 \cdot \text{H}_2\text{O}$ , and its molecular weight is 394.4. Its solubility in water is low but it is soluble in organic solvents and acidic solutions.

## PHARMACOKINETICS

Picotamide capsules gradually dissolve in the gastrointestinal tract and the drug is rapidly absorbed. After oral administration (p.o.) of 300 mg of the drug, the observed time to maximum concentrations was 0.5–0.75 h, with a mean of  $0.69 \pm 0.13$  h, indicating rapid absorption from the gastrointestinal tract (23). The peak plasma concentration was  $2.02 \pm 0.37$   $\mu\text{g/ml}$  (23).

Recent animal studies showed that picotamide diffuses from the plasma into the arterial wall and can inhibit the biological activities of  $\text{TXA}_2$  formed outside platelets. After the intravenous injection of [ $^{14}\text{C}$ ] picotamide to rabbits, radioactivity reached the arterial wall

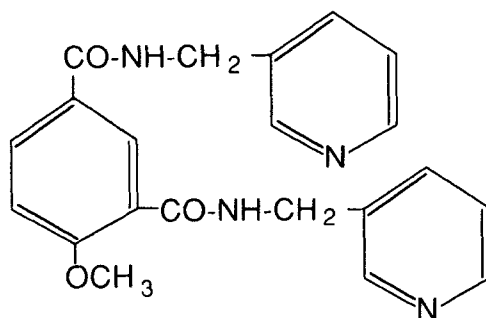


FIG. 1. Chemical structure of picotamide.

with a peak time of 116 min for the aorta and 112 min for the femoral artery, with a  $t_{1/2}$  of radioactivity disappearance of 124 and 111 min, respectively (38).

Previous studies performed with [ $^{14}\text{C}$ ]-picotamide showed that urinary and fecal excretion accounted for 46% and 43% of administered dose, respectively (51). More recently it was shown that about 30% of the dose (300 mg p.o.) was recovered as unchanged drug in the 24 h urine, mostly (about 25%) during the first 4 h after treatment (23). In rats and monkeys an important biliary elimination was found (51). The relatively low amount of the unchanged drug excreted in the urine by humans suggests that in humans the drug is also excreted in the bile.

## PHARMACOLOGY

### Antiaggregating Properties

#### *In Vitro Studies*

Picotamide was first observed to have antiaggregating properties in rabbit platelets (50), and then also in human platelets (2,3,7,15,16,28,70). In those studies picotamide was incubated with platelets for 2–3 min. It appeared to be a weak inhibitor of both  $\text{TXA}_2$ -mediated platelet aggregation ( $\text{IC}_{50}$  on platelet aggregation induced by a  $\text{TXA}_2$  analogue, U46619, was  $1.4 \times 10^{-4}$  M) and platelet  $\text{TXA}_2$  production ( $\text{IC}_{50}$  of  $1.5 \times 10^{-4}$  M), without any inhibitory effect on  $\text{PGI}_2$  synthesis (7,16,28,71). Recent studies have demonstrated that the *in vitro* antiaggregating activity of picotamide increases time-dependently. The  $\text{IC}_{50}$  for U46619 was reduced from  $6.1 \times 10^{-4}$  M at 2 min, to  $7 \times 10^{-6}$  M when picotamide was incubated for 20 min with platelets (Fig. 2). Supporting these findings, the inhibition of  $\text{TXA}_2$  formation by platelets during collagen-induced aggregation (7.5  $\mu\text{g}/\text{ml}$ ) appeared to be also time-dependent (41). Thus, the increase in the incubation time from 2 to 20 min resulted in a 2 orders of magnitude increase in the antiaggregating and anti $\text{TXA}_2$  activities of picotamide.

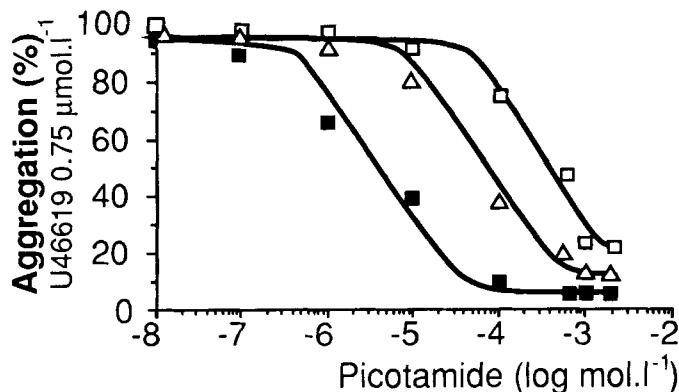


FIG. 2. Platelet aggregation induced by U46619 (0.75  $\mu\text{mol}/\text{L}$ ) with increasing concentrations of picotamide after different incubation times (empty squares = 2 minutes incubation, empty triangles = 10 minutes, filled squares = 20 minutes). Points represent mean values (from ref. 41 with permission).

### *Ex Vivo Studies*

In a pioneer *ex vivo* study on the antiaggregating activity of picotamide, Schmutzler *et al.* (62) used Breddin's method (5) to demonstrate a significant decrease in platelet aggregation after a first dose of 1500 mg/day. The antiaggregating effect further increased during the following 30 days of picotamide treatment. The *ex vivo* antiaggregating activity of picotamide was confirmed by more recent studies. Violi *et al.* reported 55% inhibition of platelet aggregation induced by collagen (4 µg/ml) after administration of picotamide to healthy subjects 600 mg twice daily (b.i.d.) for 3 days (71). TXA<sub>2</sub> formation by aggregating platelets was similarly inhibited, whereas 6-keto-PGF<sub>1</sub>α in blood samples remained unaffected (71).

The inhibitory activity of picotamide is reversible and lasts 8–12 hours after drug administration. In healthy subjects platelet aggregation induced by arachidonic acid (1 mM) or U46619 (0.5 µM) was inhibited by a single oral dose of 1000 mg picotamide from the fourth to the tenth hour (3). No effect on ADP-induced aggregation, which follows a TXA<sub>2</sub> independent pathway, was noted (3). A reduction of TXA<sub>2</sub> produced by aggregating platelets both 2 (–52%) and 8 hours (–38%) following drug administration was reported by Minuz *et al.* after administration of picotamide 300 mg three times a day (t.i.d.) for one week (36).

No correlation exists between the plasma concentration of the drug, which peaks after 2 hours (23), the inhibition of platelet aggregation, and TXA<sub>2</sub> production, which are detectable between 4 and 8–10 hours (3,36). These findings prompted initially the hypothesis that the effects of picotamide were achieved in part by a metabolite rather than the drug itself (3). Recent knowledge of the mechanism of action of picotamide indicates that picotamide *in vivo* may act as a functional noncompetitive antagonist.

### **Mechanism of Action**

Picotamide was able to inhibit dose-dependently the aggregation of aspirin-pretreated platelets (unable to produce TXA<sub>2</sub>) induced by the TXA<sub>2</sub> analogue U46619 (16,28). These results suggest that picotamide has a TXA<sub>2</sub> receptor inhibitory activity. Moreover, the decreased TXA<sub>2</sub> platelet aggregation induced by picotamide was associated with increased PGE<sub>2</sub> (28) and PGI<sub>2</sub> formation (3,28), which indicates a selective inhibitory activity of TXA<sub>2</sub> synthase (7).

Pulcinelli *et al.* (57) recently showed that picotamide inhibited both TXA<sub>2</sub> receptor effector systems. The first system is linked to phospholipase C (PLC) activation, which causes platelet aggregation and secretion, and the second mediates an increase in cytosolic Ca<sup>++</sup> and platelet shape change. In fact, at 10<sup>–4</sup> M picotamide inhibited PLC activation and caused an 80% reduction in Ca<sup>++</sup> increase caused by U46619 in platelets (57).

The direct demonstration that picotamide is a TXA<sub>2</sub>/PGH<sub>2</sub> receptor inhibitor was obtained by binding studies that showed that picotamide inhibited the binding of both agonist- ([<sup>3</sup>H]U46619) and antagonist- ([<sup>125</sup>I]PTA-OH; 9,11-dimethylmethano-11, 12-methano-16-(3[<sup>125</sup>I]-4-hydroxyphenyl)-13,14-dihydro-13-aza-15-tetranor-TXA<sub>2</sub>) TXA<sub>2</sub> analogs (37).

The binding of picotamide to a single class of TXA<sub>2</sub> receptors (with a K<sub>d</sub> of 325 nM) was recently confirmed by using radiolabelled picotamide (Fig. 3) (41). The binding of [<sup>3</sup>H]methylene-picotamide was inhibited not only by unlabelled picotamide but also by

TXA<sub>2</sub> stable analogs (Fig. 4) (41). Most importantly, picotamide can bind to the TXA<sub>2</sub> receptors in the vascular wall of human artery with the same characteristics as for binding to platelets (40). Picotamide binding to TXA<sub>2</sub>/PGH<sub>2</sub> receptors reached equilibrium rather slowly (30 min) so that after 2–3 min of incubation (the usual time of incubation for platelets in aggregation studies) only 15–20% of the total TXA<sub>2</sub> receptors per platelet at equilibrium (about 2066 per platelet) were blocked (41). This pattern agrees with the findings obtained in the studies of platelet aggregation and may explain the reported weak antiaggregating activity when platelet aggregation was assessed after 2–5 minutes of incubation (3,28).

Another relevant aspect arising from the binding studies is that picotamide behaves, at least in part, as a functionally noncompetitive receptor antagonist. Indeed, [<sup>3</sup>H]-picotamide was almost completely displaceable from the TXA<sub>2</sub> receptor during the first 30 min of incubation. After this time the binding became progressively more stable so that after 2 hours only 50% of picotamide molecules bound to TXA<sub>2</sub> receptors were displaceable. This time-dependent stable interaction of picotamide with TXA<sub>2</sub> platelet receptor mimics a noncompetitive pattern of inhibition (54). *Ex vivo* studies have confirmed the noncompetitive blockade: the *ex vivo* binding of a labelled TXA<sub>2</sub> analog remained inhibited for up to 6 hours after a single administration of 300 mg of picotamide (39). This functionally noncompetitive antagonism at the TXA<sub>2</sub>/PGH<sub>2</sub> receptor may explain the above reported discrepancy between the short half-life of picotamide in plasma (1 h) and its long-lasting (4–10 h) inhibitory effects on platelets. TXA<sub>2</sub> receptors remained occupied even when the plasma concentration of picotamide was reduced.

### ANIMAL STUDIES

Several animal studies have shown that the inhibitory effects of picotamide on either TXA<sub>2</sub> synthase or on TXA<sub>2</sub> receptor lead to reduction of mortality in animal models with enhanced TXA<sub>2</sub> formation.

In rabbits picotamide significantly reduced mortality due to endotoxin (19). Gresele *et al.* (29) showed that picotamide and aspirin were equally effective in reducing the LD<sub>50</sub>

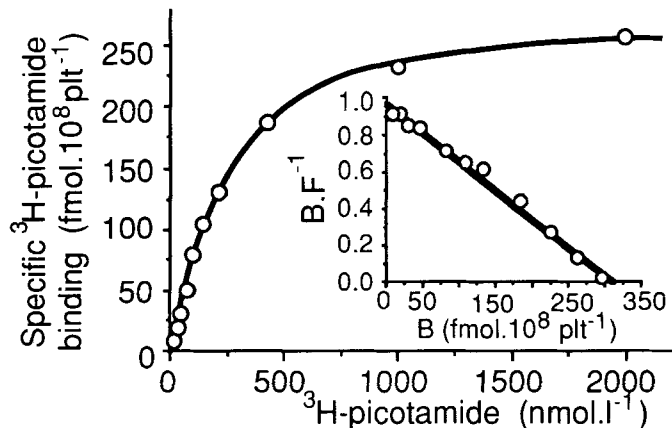
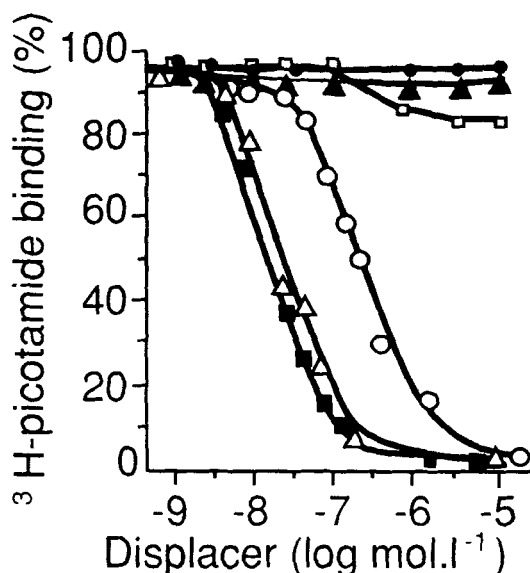


FIG. 3. Saturation curve of [<sup>3</sup>H]methylene-picotamide binding to washed human platelets at 22°C and Scatchard analysis of the binding (from ref. 41 with permission).



**FIG. 4.** Displacement of the specific [<sup>3</sup>H]methylene-picotamide binding by increasing concentrations of different compounds. Solid squares = U46619 (9,11-dideoxy-11 alpha, 9 alpha-epoxymethano-prostaglandin F2); empty triangles = ONO11120 (9,11-dimethylmethano-11,12-methane-16-phenyl-13,14- dihydro-13-aza-15-tetranor-TXA<sub>2</sub>); empty circles = picotamide; empty squares = TXB<sub>2</sub>; solid triangles = PGE<sub>2</sub>; solid circles = PGI<sub>2</sub> (from ref. 41 with permission).

of an injected collagen plus epinephrine combination. Picotamide and BM 13.505 (a TXA<sub>2</sub> receptor inhibitor), but not aspirin, reduced mortality in rats injected intravenously (i.v.) with U46619. Picotamide, but not aspirin, inhibited lethal effects of an i.v. injection of a suspension of hardened rat red blood cells, a model in which PGI<sub>2</sub> synthesis by platelets is not involved (29).

Golino *et al.* (27) tested the effectiveness of different agents known to interfere with the synthesis and/or the receptor of TXA<sub>2</sub> in abolishing the spontaneous or epinephrine-induced carotid flow variations in rabbits with experimental carotid artery stenosis and endothelial injury. A pure TXA<sub>2</sub>/PGH<sub>2</sub> receptor antagonist (SQ29548) and a selective TXA<sub>2</sub> synthase inhibitor (dazoxiben) were equally effective, in inhibiting carotid flow reduction in about 50% of treated animals. Picotamide inhibited the flow reduction in over 90% of animals, suggesting that simultaneous blockade of TXA<sub>2</sub>/PGH<sub>2</sub> receptor and inhibition of TXA<sub>2</sub> synthase are more effective than the separate inhibition of TXA<sub>2</sub> synthesis or TXA<sub>2</sub> receptor blockade (27).

## CLINICAL STUDIES

The primary criterion for testing a TXA<sub>2</sub> inhibitor in a particular disease is evidence of involvement of TXA<sub>2</sub> in the pathogenesis of the disease. In early clinical studies picotamide was used as an antiaggregating agent under clinical conditions where TXA<sub>2</sub> plays only a minor role. After initial studies were performed in patients with either peripheral vascular disease or stable effort angina, and after the specific anti-TXA<sub>2</sub> activities of the drug were identified, picotamide was used in human diseases where formation of extra-

platelet TXA<sub>2</sub> might play a definite pathophysiological role, such as unstable angina, renal failure, or inflammatory bowel disease. In these latter conditions, where a specific anti-TXA<sub>2</sub> activity is particularly important, encouraging results were obtained with picotamide.

### Peripheral Vascular Disease

Increased TXA<sub>2</sub> production in platelets has often been reported in peripheral vascular disease and picotamide has been used essentially as an antiplatelet agent. Eighteen studies on the effect of picotamide in peripheral vascular disease have been performed (1,6,8,11,12,13,14,18,20,24,30,42,50,52,56,61,64,66). Seven of these were double-blind, placebo-controlled (1,6,8,12,18,42,56) (Table 1). All studies reported an improvement in the Windsor Index and in the clinical course of the disease. The most important one was the ADEP study (1), a multicenter, randomized, double-blind, placebo-controlled study, aimed at assessing the clinical efficacy of picotamide in intermittent claudication. After a 1-month run-in period, 2304 patients were enrolled and randomly allocated to either picotamide (300 mg t.i.d.) or placebo. The occurrence of major and minor events was then recorded during an 18-month follow-up period. At the "intention to treat" analysis there was a borderline statistical difference between the two groups with respect to the cumulative major and the minor events (risk reduction 18.9%,  $p = 0.056$ ). When patients who continued treatment during the follow-up period were considered, thus performing an "on-treatment analysis," events were observed in 106 patients in the picotamide group (10.1%) compared with 140 in the placebo group (13.1%), with an overall risk reduction of 23% ( $p < 0.03$ ). A subanalysis (intention to treat analysis) of 438 diabetic patients enrolled in the ADEP study showed that picotamide significantly reduces total cardiovascular events in diabetic patients with peripheral obstructive arterial disease ( $p < 0.02$ ) (71).

Clinical efficacy of picotamide was assessed also in other small studies. An improvement in the clinical course of macro- and microangiopathic lesions and the photoplethysmographic findings at 3 and 6 months follow-up was reported by Pibiri *et al.* (56) in a

**TABLE 1.** Controlled clinical studies on the effects of picotamide in cardiovascular diseases

Author	Year	Patients enrolled	Follow-up	Study design	Parameters investigated	ANOVA test
Coto <i>et al.</i> <sup>12</sup>	1989	40	6 m	R, DB, PG, vs PL	Windsor Index	$p < 0.05$
					Walking ability	$p < 0.05$
Pibiri <i>et al.</i> <sup>56</sup>	1990	51	6 m	R, DB, PF, vs PL	Windsor Index	$p < 0.05$
					Walking ability	$p < 0.05$
Canonica <i>et al.</i> <sup>6</sup>	1991	25	3 m	R, DB, CO, vs Pl	Windsor Index	$p < 0.05$
					Walking ability	$p < 0.05$
De Falco <i>et al.</i> <sup>18</sup>	1991	87	24 m	O, PG, vsASA	Cardiovascular events	—
Balsano <i>et al.</i> <sup>1</sup>	1993	2304	18 m	R, DB, PG, vs PL	Cardiovascular events	$p < 0.029^*$
Neirotti <i>et al.</i> <sup>42</sup>	1994	20	18 m	R, DB, PG, vs PL	Pletismographic wave	$p < 0.05$
Neri Sermeri <i>et al.</i> <sup>47</sup>	1994	40	1 w	R, Db, PG, vsASA	Anginal attacks	$p < 0.05$
					Silent ischemia	$p < 0.01$
Cocozza <i>et al.</i> <sup>8</sup>	1995	50	24 m	R, DB, PG vs PL	Carotid lesion number	$p < 0.03$
					Percent stenosis	$p < 0.01$

DB = double blinded, PG = parallel groups, CO = cross over, PL = placebo, ASA = aspirin, R = randomized, O = open.

\* log-rank test for risk reduction (23%).



group of 51 diabetic patients treated with picotamide 600 mg/day in comparison to the placebo group. These results were confirmed in a group of 20 non-diabetic atherosclerotic patients (stage II according to Fontaine) treated with picotamide 300 mg t.i.d. compared with the placebo group (42). Three double-blind, placebo-controlled studies (6,12,56) reported a significant improvement in the walking distance in patients who received picotamide (600–900 mg/day) compared with placebo (+ 23% and – 40%, respectively).

A recent double-blind, placebo-controlled study showed that long-term treatment (24 months) with picotamide slows the evolution of carotid atherosclerotic lesions (8). After 24 months, the number of carotid lesions ( $p < 0.03$ ) and percent stenosis ( $p < 0.01$ ) were significantly lower in the picotamide than in the randomized placebo group (8).

### **Myocardial Ischemia and Unstable Angina**

Recent studies provided evidence that unstable angina may be sustained by an acute immune-mediated inflammatory reaction (33,46). Lymphocytes and monocytes were activated (46), with increased  $\text{TXA}_2$  formation even in the presence of aspirin-blocked platelets (43,45), suggesting an extraplatelet source of  $\text{TXA}_2$ . Moreover, in patients with unstable angina no relationship was found between the amount of  $\text{TXA}_2$  produced by platelets (measured by assessing 1–3 dinor  $\text{TXB}_2$ , a metabolite of  $\text{TXB}_2$  of platelet origin) and anginal episodes (69), indirectly suggesting that platelet activation is not necessarily a primary event in myocardial ischemia. Monocytes from patients with active unstable angina produce an increased amount of  $\text{TXA}_2$  (47) when compared with monocytes from patients in the inactive phase. The effects of picotamide were compared with those of aspirin in a pilot study in unstable angina (47). Picotamide, but not aspirin, controlled myocardial ischemia (anginal attacks – 84.8%, silent ischemic episodes – 64.2% and overall duration of ischemia – 69.8%), although aspirin inhibited platelet  $\text{TXA}_2$  production more than picotamide. The results of this study indicate that picotamide can control myocardial ischemia that is mainly due to  $\text{TXA}_2$  formed by monocytes in the atherosclerotic plaque, whereas aspirin at the usual therapeutic dose (324 mg/day) is unlikely to reach the extravascular sites in acetylated form. Indeed, aspirin is rapidly deacetylated by the esterases in plasma and the liver. In an open study performed on 19 patients with stable effort angina, picotamide (900 mg/day for 10 months) significantly reduced the mean nitrate consumption (48).

### **Renal Disease**

Increased  $\text{TXA}_2$  generation has been reported in different renal diseases and may contribute to glomerular damage (4,53,65). In patients with type II diabetes with microalbuminuria at rest, short term administration of picotamide (900 mg/day for 10 days) was associated with a reduction in albuminuria after exercise (25). In a small prospective study performed on 6 diabetic patients (9-month treatment), picotamide reduced proteinuria at the 3, 6, and 9-month follow-up tests (26).

In renal transplantation  $\text{TXA}_2$  may play a role, as suggested by the increased urinary excretion of  $\text{TXA}_2$  metabolites reported in patients with acute graft rejection (22). In a randomized, double-blind, placebo-controlled study performed on 36 renal transplant patients, prolonged picotamide treatment (600 mg/day for 1 year) significantly reduced urinary excretion of  $\text{TXB}_2$  and improved renal function. After one year of picotamide

treatment, the mean plasma concentration of creatinine decreased in the picotamide group ( $-14.2 \pm 3.9 \mu\text{mol/l}$  vs baseline) but not in the placebo group ( $+13.5 \pm 5.2 \mu\text{mol/l}$  vs baseline) (58,59).

### Inflammatory Bowel Disease

Although the etiology of inflammatory bowel disease remains obscure, there is a growing body of evidence suggesting a possible role of  $\text{TXA}_2$  (32,34). In Crohn's disease  $\text{TXA}_2$  is produced in excess not only in inflamed mucosa but also by normal bowel and by isolated intestinal and peripheral blood mononuclear cells (60). After the initial studies in animal models, where  $\text{TXA}_2$  inhibitors showed beneficial effects, picotamide has been recently tested in inflammatory bowel disease in humans. In a clinical trial performed in 9 patients with Crohn's disease, picotamide (600 mg b.i.d.) inhibited colonic mucosal generation of  $\text{TXB}_2$  and improved the clinical course of the disease (diarrhea and abdominal pain) (9,10).

### SIDE EFFECTS

Picotamide was well tolerated even in studies with long follow-up periods. The side effects in the picotamide group of the ADEP study (1) were assessed by monitoring the adverse reactions (ADRs, classified according to the World Health Organization coding system) in terms of their severity, duration, relationship to treatment, evolution, and consequences, and were reported in a separate study (72). ADRs in the picotamide group did not differ from those in the placebo group. In particular, 165 out of 1150 patients (14.3%) on picotamide and 156 out of 1154 (13.5%) on placebo complained of at least one ADR. The total number of ADRs reported in the case report forms were 240 for picotamide and 239 for placebo. The most frequent ADRs were gastrointestinal disturbances, predominantly abdominal pain (8.2% for picotamide and 8.5% for placebo). Others were nausea (1.6% for picotamide and 1.0% for placebo), headache (1.4% and 0.8%), and pruritus (1.1% and 0.8%).

### CONCLUSIONS

In conclusion, picotamide is a  $\text{TXA}_2$  antagonist that inhibits the synthesis of  $\text{TXA}_2$  at the synthase level and its effect at the receptors. Although its clinical efficacy appears promising in different human diseases, larger clinical studies are needed to definitively assess its efficacy in clinical conditions where platelet and extraplatelet  $\text{TXA}_2$  play relevant roles. If large clinical trials confirm its clinical efficacy, picotamide might replace classical cyclooxygenase inhibitors in the treatment of vascular, renal, and inflammatory bowel diseases.

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