

Treatment of arterial hypertension with tienilic acid, a new diuretic with uricosuric properties

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Tienilic acid — 2,3-dichloro-4-(2-thienyl-carbonyl)phenoxyacetic acid — is a new diuretic with uricosuric properties. Nineteen patients with moderate arterial hypertension were treated for 5 consecutive weeks in a randomized fashion in a double-blind study with either tienilic acid or hydrochlorothiazide. Blood pressure was significantly reduced and to the same degree with both drugs. In 7 of the 11 patients receiving tienilic acid the daily dose was increased from 250 to 500 mg after 2 weeks, and in 2 of the 8 patients taking hydrochlorothiazide the daily dose was increased from 50 to 100 mg. Because of the potent uricosuric action of tienilic acid the mean serum urate concentration decreased from 6.3 to 3.3 mg/dL in the patients taking the drug. In contrast, in the patients receiving hydrochlorothiazide the mean serum urate concentration increased from 6.1 to 7.8 mg/dL. Moderate hypokalemia of almost identical degree (mean serum potassium values 3.6 and 3.5 mmol/L) and mild metabolic alkalosis were observed in both groups. Tienilic acid had a marked hypocalciuric effect, which was of the same magnitude as that observed with hydrochlorothiazide. During the 5 weeks of treatment no significant change in renal or liver function was observed in either group. There were no hematologic complications and the drug was remarkably well tolerated. Tienilic acid, because of its unique character as a diuretic, hypouricemic and antihypertensive agent, should become the preferred drug for the treatment of arterial hypertension.

L'acide tiénilique — acide 2,3-dichloro-4-(2-thienyl-carbonyl)phenoxyacétique — est un nouveau diurétique qui possède des propriétés uricosuriques. Dix-neuf patients souffrant d'hypertension artérielle modérée ont été répartis au hasard et traités durant 5 semaines consécutives avec de l'acide tiéniliq ou de l'hydrochlorothiazide au cours d'une étude à double insu. La tension artérielle systolique et diastolique s'est abaissée de façon significative

et au même degré avec l'une ou l'autre drogue. Chez 7 des 11 patients recevant de l'acide tiéniliq la dose quotidienne a été augmentée de 250 à 500 mg après 2 semaines de traitement, et chez 2 des 8 patients recevant de l'hydrochlorothiazide la dose quotidienne a été augmentée de 50 à 100 mg. L'uricémie est passée de 6.3 à 3.3 mg/dL chez les patients recevant de l'acide tiéniliq à cause de l'action uricosurique puissante de la drogue. Par contraste, l'uricémie est passée de 6.1 à 7.8 mg/dL chez les patients recevant de l'hydrochlorothiazide. Une hypokaliémie presque identique (taux moyens de potassium sérique 3.6 et 3.5 mmol/L) et une alcalose métabolique légère ont été observées chez les deux groupes. L'acide tiéniliq possède une action hypocalciurique de même intensité que celle observée avec l'hydrochlorothiazide. Durant les 5 semaines de traitement aucun changement dans la fonction rénale ou hépatique n'est survenu chez les deux groupes. Aucune complication à caractère hémalogique n'a été observée et la drogue a été remarquablement bien tolérée. À cause de son caractère particulier comme agent diurétique, uricosurique et antihypertensif, l'acide tiéniliq est appelé à jouer un rôle de premier plan dans le traitement de l'hypertension artérielle.

Tienilic acid — 2,3-dichloro-4-(2-thienyl-carbonyl)phenoxyacetic acid — is a newly synthesized diuretic¹ that has been found to have uricosuric properties in humans,^{2,3} dogs,^{3,4} rats⁴ and mice.¹ The drug has been used in Europe to treat arterial hypertension and found to be effective.⁵⁻⁸ Its effectiveness was recently confirmed in North America by Nemati, Kyle and Freis.⁹

The natriuretic effect of tienilic acid apparently takes place in the cortical diluting segment of the distal tubule^{10,11} and is independent of its uricosuric action, which takes place in the proximal tubule in dogs.⁴ In these animals the drug and paraaminohippurate (PAH) compete.⁴ Therefore, at least in dogs, PAH clearance cannot be used to measure renal plasma flow during the administration of tienilic acid.

We have characterized the metabolic effects of tienilic acid in normal humans.^{2,3} In addition to the uricosuric effect with resulting hypouricemia the drug can cause moderate hypokalemia, metabolic alkalosis and hypocalciuria without a change in the serum calcium concentration when taken for 7 days.^{2,3}

The study reported below was undertaken to investigate the effect of tienilic acid on moderate arterial hypertension and to compare this effect with that of hydrochlorothiazide, thiazides being the type of diuretic most widely used in the treatment of hypertension.

Methods

Nineteen ambulatory patients with moderate arterial hypertension were treated in a randomized fashion in a double-blind study. The 7 women and 12 men ranged in age from 28 to 60 years. Five other patients entered the study but were excluded prior to treatment either because their blood pressure fell to normal with placebo administration or because of poor cooperation.

Intravenous pyelograms were either normal or revealed questionable calyceal changes except in two patients, one with bilateral stenosis of the renal arteries and the other with stenosis of the left renal artery as revealed by renal arteriography. No patient had evidence of hematologic, hepatic or degenerative renal disease, or of diabetes mellitus. No patient had been taking reserpine or anticoagulants, and the use of any other drug during the study was not permitted. The patients were informed of the nature of the study and all provided written consent.

All patients underwent complete history-taking and physical examination, electrocardiography, chest roentgenography and studies of blood, plasma and urine. No patient received a potassium supplement during the study. All came to the renal clinic once a week for 11 consecutive weeks for clinical and laboratory assessment.

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The study began with a 1-week "wash-out" period, during which the patients received no medication. The patients then received placebo for 3 weeks. Pill counts and interviews were used throughout the study to assess drug intake. Following completion of the placebo period the patients were randomly assigned in a double-blind fashion to take either tienilic acid (one 250-mg tablet daily) or hydrochlorothiazide (one 50-mg tablet daily). The daily dose was doubled if the blood pressure failed to decrease after 2 weeks. The placebo, tienilic acid (SKF 62698, Smith Kline & French Canada Ltd.) and hydrochlorothiazide tablets had exactly the same appearance. The tablets were taken after breakfast for 5 consecutive weeks, then the drug was discontinued for 2 weeks, during which the patients took no other medication. The patients were on a free diet; no attempt was made to curtail sodium intake.

The patients were weighed and their blood pressure and pulse rate recorded at each visit by a registered nurse trained for this project. Blood pressure was measured in the right arm with a mercury sphygmomanometer three times each with the patient supine and standing at 1-minute intervals. Before the blood pressure was taken the patients were supine for 5 minutes and standing for 3 minutes. Diastolic blood pressure was recorded as the level at which the Korotkoff sounds disappeared completely.

The laboratory methods used in this study have previously been described.^{2,4} A 24-hour urine specimen was collected the day prior to the weekly visit and kept under mineral oil in containers provided by the clinic. Urinalysis was performed on freshly collected specimens by highly trained technicians of the renal laboratory under our supervision.

Statistical analysis was performed with Student's *t*-test for paired data. *P* values of less than 0.05 were considered significant. Unless otherwise indicated, all values in the tables are means \pm the standard error of the mean.

Results

Dosage

Tienilic acid was taken by 11 patients and hydrochlorothiazide by 8. The two groups of patients were almost identical with regard to mean age (44 and 43 years respectively) and mean blood pressure recorded with the patient supine during the period of placebo administration (168/103 and 166/104 mm Hg). The only difference was the known duration of hypertension, which was greater in the patients treated with tienilic acid (means 9.6 and 5.2 years). After 2 weeks of therapy the daily dose of tienilic acid was increased to two 250-mg tablets in 7 of the 11 patients because of inadequate reduction in blood pressure. The daily dose of hydrochlorothiazide was increased to two 50-mg

tablets in two of the eight patients for the same reason.

Blood pressure

Tienilic acid and hydrochlorothiazide had a similar reducing effect on the systolic and diastolic blood pressure (Table I). With tienilic acid therapy the mean maximal decreases in blood pressure were 18 mm Hg for the systolic pressure and 9 mm Hg for the diastolic with the patient supine, and 21 and 12 mm Hg respectively with the patient standing. With hydrochlorothiazide therapy the mean maximal decreases were 25 and 15 mm Hg with the patient supine and 22 and 12 mm Hg with the patient standing. The slight differences between the two drugs were not significant.

Heart rate

There was no significant change in heart rate in either group although, as expected, the rate tended to be higher when the patient was standing.

Uric acid values

During the administration of tienilic acid the mean serum urate concentration fell from 6.3 to 3.3 mg/dL (Table II). Although the uricosuric effect of tienilic acid has been well established for humans,^{2,3} it was less pronounced in this study, in which a 24-hour collection of urine was examined only once a week. However, the ratio of urate clearance to endo-

Table I—Changes in blood pressure with tienilic acid or hydrochlorothiazide therapy

| Drug, body position and blood pressure | Mean blood pressure \pm standard error of the mean (mm Hg) | | | | | | | |
|--|--|----------------|--------------|--------------|--------------|--------------|---------------|--------------|
| | Placebo period | Treatment week | | | | | Recovery week | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 |
| Tienilic acid | | | | | | | | |
| Supine | | | | | | | | |
| Systolic | 168 \pm 6 | 158 \pm 8 | 158 \pm 8 | 152 \pm 7* | 155 \pm 7* | 150 \pm 9* | 154 \pm 12 | 156 \pm 7* |
| Diastolic | 103 \pm 3 | 98 \pm 4 | 101 \pm 5 | 94 \pm 5* | 96 \pm 5* | 98 \pm 5 | 95 \pm 7* | 98 \pm 4 |
| Standing | | | | | | | | |
| Systolic | 166 \pm 5 | 157 \pm 7 | 156 \pm 7 | 145 \pm 8* | 150 \pm 7* | 148 \pm 8* | 154 \pm 10 | 158 \pm 6 |
| Diastolic | 107 \pm 3 | 104 \pm 4 | 104 \pm 4 | 98 \pm 5* | 100 \pm 4* | 95 \pm 5* | 101 \pm 5* | 102 \pm 4 |
| Hydrochlorothiazide | | | | | | | | |
| Supine | | | | | | | | |
| Systolic | 166 \pm 3 | 155 \pm 5 | 148 \pm 5* | 144 \pm 5* | 141 \pm 6* | 146 \pm 5* | 152 \pm 4 | 156 \pm 6 |
| Diastolic | 104 \pm 4 | 100 \pm 3 | 94 \pm 3* | 94 \pm 2* | 89 \pm 3* | 95 \pm 2 | 92 \pm 3* | 98 \pm 4 |
| Standing | | | | | | | | |
| Systolic | 162 \pm 4 | 147 \pm 6* | 143 \pm 5* | 140 \pm 6* | 145 \pm 5* | 141 \pm 4* | 154 \pm 5 | 157 \pm 7 |
| Diastolic | 107 \pm 3 | 100 \pm 4* | 96 \pm 2* | 99 \pm 3* | 95 \pm 2* | 95 \pm 3* | 101 \pm 3* | 102 \pm 4 |

*Significantly different (*P* < 0.05) from value during placebo period.

genous creatinine clearance increased during the last 2 weeks of treatment. With hydrochlorothiazide therapy the serum urate concentration rose from 6.1 to 7.8 mg/dL and the clearance ratio decreased (Table II). When either drug was discontinued the serum urate concentration rose rapidly above values in the placebo period for the tienilic acid group and fell to values in the placebo period for the hydrochlorothiazide group.

Electrolyte values and acid-base balance

The serum sodium concentration was unchanged in both groups. The serum potassium concentration fell significantly, to a mean of 3.6 mmol/L with tienilic acid and 3.5 with hydrochlorothiazide therapy (Table III), but returned to values in the placebo period after discontinuation of either drug. In both groups the serum chloride concentration fell by a mean of 5 mmol/L and rose to values in the placebo period after cessation of therapy. The serum bicarbonate concentration rose by a mean of 4.4 mmol/L in the tienilic

acid group and 4.1 mmol/L in the hydrochlorothiazide group. The mild metabolic alkalosis noted during drug administration disappeared completely after discontinuation of either drug (Table III). The serum magnesium and blood glucose concentrations did not vary significantly during the study.

Excretion of electrolytes and hydrogen ion

Sodium and chloride excretion varied from week to week and correlated with changes in body weight. Potassium excretion was more constant and averaged 62 mmol/24 h in both groups. These values were not different from those during the placebo period but were relatively high in view of the falling serum potassium concentration. The urinary magnesium excretion averaged 3.8 mmol (7.6 meq)/24 h in the tienilic acid group and 3.75 mmol (7.5 meq)/24 h in the hydrochlorothiazide group. These values were not significantly different from values in the placebo period. The urinary pH averaged 6.10 in each group

during treatment, a value similar to that in the placebo period. Excretion of titratable acid, ammonia and bicarbonate was also unchanged, so that the net acid excretion (titratable acid + ammonia - bicarbonate) remained stable.

Calcium and phosphorus values

Tienilic acid and hydrochlorothiazide therapy had no effect on serum calcium and phosphorus concentrations. However, as Table IV shows, both drugs had a hypocalciuric effect. The decrease in urinary calcium excretion reached 40% with tienilic acid and 52% with hydrochlorothiazide therapy; this difference was not significant. Urinary calcium excretion rose following discontinuation of either drug. No significant change in urinary phosphorus excretion was observed.

Renal function

A slight but significant increase in mean blood urea nitrogen concentration was noted during treatment with each drug, from 14 to 19 mg/dL with tienilic acid and from 15 to

Table II—Changes in serum urate concentration and excretion

| Variable and drug | Mean \pm standard error of the mean | | | | | | | |
|--|---------------------------------------|------------------|-----------------|-----------------|------------------|-----------------|-----------------|-----------------|
| | Placebo period | Treatment week | | | | | Recovery week | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 |
| Serum urate concentration (mg/dL) | | | | | | | | |
| Tienilic acid | 6.3 \pm 0.4 | 4.3 \pm 0.3* | 4.3 \pm 0.3* | 3.4 \pm 0.3* | 3.3 \pm 0.3* | 3.6 \pm 0.3* | 6.9 \pm 0.6 | 6.8 \pm 0.5 |
| Hydrochlorothiazide | 6.1 \pm 0.6 | 7.6 \pm 0.7* | 7.4 \pm 0.8* | 7.8 \pm 1.0* | 7.4 \pm 0.7* | 7.8 \pm 1.0* | 6.8 \pm 0.4 | 6.2 \pm 0.6 |
| Urate clearance/ endogenous creatinine clearance | | | | | | | | |
| Tienilic acid | 0.12 \pm 0.02 | 0.11 \pm 0.02 | 0.15 \pm 0.04 | 0.14 \pm 0.04 | 0.21 \pm 0.05* | 0.16 \pm 0.05 | 0.10 \pm 0.04 | 0.06 \pm 0.01 |
| Hydrochlorothiazide | 0.12 \pm 0.02 | 0.08 \pm 0.01* | 0.10 \pm 0.04 | 0.11 \pm 0.02 | 0.07 \pm 0.02* | 0.08 \pm 0.02 | 0.08 \pm 0.02 | 0.08 \pm 0.02 |

*Significantly different ($P < 0.05$) from value during placebo period.

Table III—Changes in serum potassium, chloride and bicarbonate concentrations

| Serum constituent and drug | Mean concentration \pm standard error of the mean (mmol/L) | | | | | | | |
|----------------------------|--|----------------|----------------|-----------------|-----------------|-----------------|----------------|----------------|
| | Placebo period | Treatment week | | | | | Recovery week | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 |
| Potassium | | | | | | | | |
| Tienilic acid | 4.2 \pm 0.1 | 4.0 \pm 0.2 | 4.0 \pm 0.2 | 3.6 \pm 0.1* | 3.7 \pm 0.2* | 3.7 \pm 0.1 | 4.1 \pm 0.1 | 4.3 \pm 0.1 |
| Hydrochlorothiazide | 4.3 \pm 0.1 | 3.8 \pm 0.1* | 3.9 \pm 0.1* | 3.5 \pm 0.1* | 3.8 \pm 0.1* | 3.6 \pm 0.1* | 4.2 \pm 0.1 | 4.2 \pm 0.1 |
| Chloride | | | | | | | | |
| Tienilic acid | 103 \pm 0.5 | 100 \pm 0.7* | 100 \pm 2.4 | 99 \pm 1.2* | 99 \pm 1.2* | 98 \pm 1.0* | 105 \pm 0.8 | 104 \pm 0.5 |
| Hydrochlorothiazide | 103 \pm 0.4 | 98 \pm 1.8* | 98 \pm 1.2* | 98 \pm 0.7* | 98 \pm 0.7* | 98 \pm 1.3* | 103 \pm 2.0 | 103 \pm 1.0 |
| Bicarbonate | | | | | | | | |
| Tienilic acid | 27.7 \pm 0.8 | 29.3 \pm 0.8 | 29.0 \pm 0.9 | 29.0 \pm 1.0 | 28.3 \pm 1.2 | 32.1 \pm 1.4* | 26.0 \pm 1.3 | 27.5 \pm 1.7 |
| Hydrochlorothiazide | 26.2 \pm 0.7 | 27.7 \pm 1.2 | 29.3 \pm 1.9 | 30.3 \pm 0.8* | 29.6 \pm 1.2* | 28.8 \pm 1.0* | 28.9 \pm 1.5 | 27.3 \pm 0.5 |

*Significantly different ($P < 0.05$) from value during placebo period.

Table IV—Changes in urinary calcium excretion

| Drug | Mean excretion \pm standard error of the mean (mg/24 h) | | | | | | | |
|---------------------|---|----------------|---------------|---------------|---------------|---------------|---------------|--------------|
| | Placebo period | Treatment week | | | | | Recovery week | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 |
| Tienilic acid | 221 \pm 25 | 134 \pm 31* | 153 \pm 25* | 111 \pm 16* | 142 \pm 23* | 133 \pm 21* | 177 \pm 32 | 154 \pm 20 |
| Hydrochlorothiazide | 149 \pm 20 | 96 \pm 11* | 94 \pm 10* | 79 \pm 7* | 71 \pm 12* | 81 \pm 6* | 148 \pm 28 | 116 \pm 17 |

*Significantly different ($P < 0.05$) from value during placebo period.

18 mg/dL with hydrochlorothiazide. The concentration fell to values in the placebo period after discontinuation of either drug. The serum creatinine concentration remained unchanged throughout the study in both groups, as did the 24-hour clearance of endogenous creatinine.

Urinalysis results

No significant change in findings was noted during the study except that one patient taking hydrochlorothiazide had transient proteinuria (protein excretion 1.0 g/24 h) during the second week of treatment.

Liver function

Serum concentrations of bilirubin, cholesterol, alkaline phosphatase, glutamic oxaloacetic transaminase and lactate dehydrogenase were remarkably stable throughout the study in each group.

Hematologic findings

Blood hemoglobin concentration and leukocyte count were stable throughout the study in each group. The platelet count increased significantly during treatment, from $242 \times 10^9/L$ to $266 \times 10^9/L$ in the tienilic acid group and from $251 \times 10^9/L$ to $276 \times 10^9/L$ in the hydrochlorothiazide group during the second week of treatment only. These values fell during the ensuing weeks towards values in the placebo period.

Electrocardiographic findings

Electrocardiograms (ECGs) were performed on each patient at regular intervals. Of the 11 patients taking tienilic acid 7 had a normal ECG, 2 having persistent bradycardia, 3 had persistent signs of left ventricular hypertrophy and 1 had changes in T-waves and ST-segments compatible with myocardial ischemia, which disappeared after treatment was discontinued. At the time the ischemic

changes were noted the patient's serum potassium concentration was 3.5 mmol/L. Of the eight patients taking hydrochlorothiazide five patients had a normal ECG throughout the study, two had persistent signs of left ventricular hypertrophy and one had transient ventricular extrasystoles with a serum potassium concentration of 4.1 mmol/L.

Side effects

In general both medications were well tolerated. In the tienilic acid group eight patients had no complaints, two complained of fatigue, one of whom also had nausea in the morning, and another complained of dizziness, perspiration and numbness of the fingers of the left hand when his serum potassium concentration was 3.0 mmol/L. In the hydrochlorothiazide group six patients had no complaints, one complained of fatigue and another complained of bilateral tinnitus during the fifth week of drug administration. There was no evidence of hearing impairment in any patient in either group.

Discussion

This study has demonstrated that tienilic acid, a new diuretic with uricosuric action, is as effective as hydrochlorothiazide in the treatment of moderate arterial hypertension. The results were in accord with those reported recently by Nemati and colleagues.⁹ The ideal dose appears to be 500 mg/d, although some patients may respond to 250 mg/d. It has been shown by others that there is no advantage in increasing the daily dose above 500 mg and that higher daily doses may be associated with undesirable side effects.⁸

In all patients receiving tienilic acid hypouricemia developed. This is related to the marked uricosuric effect of the drug, an effect that oc-

curs in healthy humans,^{2,3} dogs⁴ and rats⁴ but was difficult to demonstrate in this study because 24-hour collections of urine could not be obtained continuously throughout the study.

The administration of tienilic acid for 5 weeks led to moderate hypokalemia and metabolic alkalosis and a proportional decrease in the serum chloride concentration. These effects were also noted with hydrochlorothiazide administration. We have previously demonstrated that potassium and net acid excretion increase significantly during the administration of tienilic acid in the same daily dose to healthy individuals.^{2,3} In this study we could not detect a significant change in net acid excretion during the administration of either tienilic acid or hydrochlorothiazide, again probably because we could not obtain 24-hour collections of urine each day during the study. However, the daily excretion of potassium, which was unchanged from that observed during the placebo period, was high relative to the falling serum concentration.

The effect of tienilic acid on urinary calcium excretion was unmistakable and confirms our previous observation in healthy individuals.^{2,3} The hypocalciuric effect was about the same or slightly less than that of hydrochlorothiazide. Hence tienilic acid can be taken to reduce urinary calcium excretion. No effect on urinary phosphorus excretion was noted and the serum calcium concentration remained normal during the 5 weeks of drug administration.

The slight increase in blood urea nitrogen concentration observed during both tienilic acid and hydrochlorothiazide therapy is best attributed to slight dehydration caused by the diuretic effect of each drug, for the serum creatinine concentration and the endogenous creatinine clearance,

which are much better indices of renal function, did not change during the administration of either drug. Therefore, with adequate initial renal function, tienilic acid can be safely administered for 5 weeks. The drug does not appear to be hepatotoxic over the same period if liver function is initially normal. No hematologic complications were noted in our patients during administration of tienilic acid. The increase in platelet count was very small and only significant during the second week of treatment.

As a direct complication of tienilic acid administration one could expect that the proximal tubular blockade of urate⁴ could lead to precipitation of uric acid in the tubules and to formation of uric acid stones in the urinary tract. However, hyperuricosuria in absolute terms probably occurs only at the beginning of treatment or when the dose of the drug is increased. Furthermore, the lack of these complications is probably also due to the natriuretic effect of the drug, with the resulting high urine volume and dilution of urate. Finally, when the serum urate concentration is substantially reduced the uric acid excretion may be high relative to the serum concentration but normal or low in absolute terms. These considerations probably explain the lack of reported complications of the drug secondary to urate excretion.⁵⁻⁹

In this study the side effects noted in a few patients were nonspecific and can be observed with any other diuretic.

Tienilic acid has the advantage over currently available diuretics of an important uricosuric action. This effect is desirable in view of the high-risk factor represented by hyperuricemia,¹²⁻¹⁴ a condition found relatively frequently in hypertensive individuals before treatment,¹⁵⁻¹⁷ especially in those who are obese.¹⁸⁻²⁰ The currently available diuretics induce hyperuricemia,^{21,22} and when this condition is present before treatment its severity may increase greatly. Xanthine oxidase inhibitors are usually given in conjunction with diuretics when the patient has hyperuricemia. Aside from its being a high-risk factor for coronary artery and other vascular disease^{12,13} hyperuricemia can lead to attacks of gouty arthritis during diuretic therapy.²³ In the fu-

ture this problem can be avoided with the use of tienilic acid. However, studies of longer duration are needed to evaluate fully the safety and usefulness of tienilic acid in the treatment of arterial hypertension and other conditions. When these are well established, tienilic acid, because of its uricosuric activity, should become the preferred diuretic for the treatment of hypertension.

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