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REVIEW

Theobromine for treatment of uric acid stones and other diseases

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Summary ***Theobromine (or 3,7-dimethylxanthine) is a natural alkaloid present in cocoa plant and its derivatives, such as chocolate. About 20% of ingested theobromine is excreted unchanged in the urine. Theobromine also derived from caffeine that is metabolized into theobromine by 12%. The primary metabolites of theobromine are 3-methylxantine, 7-methylxantine, 7-methyluric acid and 3,7-dimethyluric acid. Theobromine has an inhibitory activity of uric acid crystallization, because it has a structural pattern very similar to uric acid and can substitute uric acid molecules in the corresponding uric acid crystals, making them longer and thinner and decreasing their growth rate. Theobromine also favors the dissolution of crystals by decreasing supersaturation of uric acid by forming aggregates with uric acid through hydrogen bonds and aromatic stacking interactions (-stacking bonds) increasing urinary solubility of uric acid. Theobromine can be used for uric acid stone dissolution in combination with alkalinization to reduce the dose of citrate, thus preventing excessive alkalinization and the risk of formation of sodium urate crystals. Theobromine could also be used to treat patient with xanthine stones that cannot be dissolved by alkalinization because the solubility of xanthine is relatively independent of urinary pH. A metabolite of theobromine, 7-methylxanthine, has the potential to be used for the prevention of the formation of sodium urate crystals in the synovial fluid of gouty patients.***

KEY WORDS: Theobromine; Uric acid; Urinary calculi; Xanthine; Gout.

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INTRODUCTION

Theobromine (or 3,7-dimethylxanthine) is a natural alkaloid present in Theobroma cacao (cocoa plant) and its derivatives. It is found in chocolate, and it is also present in small quantities in tea leaves (1, 2).

Chemically it is a xanthine, a derivative of purine, whose related compounds include theophylline, caffeine, paraxanthine, and 7-methylxanthine, each of which differ in the number or placement of the methyl groups. Theobromine is derived from the nucleoside xanthosine by cleavage of the ribose and N-methylation to 7-methylxanthosine.

Theobromine is slightly water-soluble but more fat-soluble, therefore requires 2-3 hours to peak, while caffein is highly water-soluble and peaks after only 30 minutes.

In the liver, it is metabolized into xanthine and subsequently into methyluric acid.

The elimination half-life of theobromine is between 6 and 8 hours. The primary metabolites of theobromine are 3-methylxantine, 7-methylxantine, 7-methyluric acid and 3,7-dimethyluric acid, with 18-21% of theobromine excreted unchanged in the urine (3-5).

Theobromine also derives from caffeine that is metabolized in the liver into paraxanthine (84%), theobromine (12%), and theophylline (4%). For this reason, individuals that non ingest theobromine (or chocolate) could have low, though detectable, urinary levels of theobromine (6, 7).

Theobromine has stimulating action on the central nervous system by intervening on the synapses, but this effect is weaker than caffeine (8).

It has negligible toxicity in humans, because it is metabolized very quickly. In other mammals, such as dogs and cats, it becomes toxic because they metabolize theobromine very slowly. The symptoms of intoxication are excitation, lowered heart rate, convulsions and in the most serious cases death (9).

Theobromine has several various pharmacological applications including cough suppression, increase of plasma HDL cholesterol and decrease of plasma LDL cholesterol, protection of enamel surface (10-13). A derivative of theobromine, 7-methylxanthine, has been used for the treatment of myopia (14).

Theobromine should be administered as extract of cocoa beans rather than chocolate that contains large amounts of sugar and oxalate, that should be avoided in subjects with diabetes type 2 or metabolic syndrome and calcium oxalate renal stone formers.

TREATMENT AND PREVENTION OF URIC ACID STONES

Uric acid urinary stones account for about 10% of all the urinary stones although it is predictable an increase of their prevalence because of demographic and climate changes (15, 16).

Uric acid stones form by crystallization of urinary uric acid when its concentration is above the threshold of solubility which depends on pH. It ranges from 110 mg/L for urinary pH below 5.0 to 250 mg/L for pH 5.5 and up to 600 mg for a pH over 6.0.

Urinary saturation for uric acid depends on urinary pH and urinary uric acid concentration (17-19). When urine is supersaturated with respect to uric acid, crystal formation is possible, although above this threshold there is an interval of saturation values at which the solution is

metastable that means that preformed crystals can grow but there is no formation of new crystals. Above the upper limit of the metastable zone of saturation crystals form spontaneously. Other factors can interfere with uric acid crystallization in the urine as the presence of heterogeneous nuclei that can facilitate crystal formation or inhibitors of crystallization. Uric acid stones can be dissolved when urinary saturation is under the threshold of supersaturation.

Alkalinization

Alkalinization by high doses of citrate and bicarbonate is commonly used for uric acid dissolution (20). Urinary pH should be raised over 6, although higher values are not recommended because a urinary pH above 6.2 can cause the formation of an outer shell of insoluble calcium phosphate salts that are less soluble for higher pH values. Furthermore, in the presence of hyperuricosuria, deposits of sodium and/or potassium urate can form, because of reduced solubility of such urate salts at higher pH values (contrary to what happens for uric acid). Finally, long-term treatment with citrate can cause gastrointestinal disturbances.

Other substances

N-acetylcysteine (NAC) has been proposed for its alkalinizing and mucolytic effect due to the cleavage of disulfide bridges of mucoproteins contained in the deposits of organic matter covering stone crystals (21, 22).
In vitro studies suggested the use of some glycosaminoglycans, glycoproteins and saponins (such as ginseng extract) to interfere with crystallization of uric acid (23). However, these substances are not properly inhibitors because they act by modifying the surface tension of water and do not show dose-response relationships.

Theobromine

More recently, *in vitro* studies showed that theobromine is a very effective inhibitor of uric acid crystallization (24, 25). This effect is clinically significant for urinary concentration over 15 mg/L or higher, although higher concentrations (80 mg/L) provided no additional benefit.
Urinary concentrations in the therapeutical range are obtained after oral administration of 300 mg of theobromine with approximately 60 mg excreted unchanged in the urine. Caffeine, theophylline and paraxanthine showed no similar effects. In fact, they had a structure very similar to theobromine, but minimal modification of their chemical structure makes them ineffective as inhibitors. Theobromine inhibits nucleation of uric acid crystals being absorbed onto the faces of the crystals and modifying their morphology making them longer and thinner. In particular, theobromine may inhibit growth at only one of the faces of the crystal (210), but not at the others (001 and 201). Because uric acid and theobromine molecules have very similar structural patterns, theobromine can substitute uric acid molecules in the corresponding uric acid crystals. The incorporation of this molecule to the uric acid crystal lattice modifies the structure of some layers so increasing their energy and decreasing their growth rate. In the presence of theobromine crystals formed on the surface of the uric acid were smaller. Thus, theobromine may be clinically useful in preventing the regrowth of uric acid calculi fragments. Theobromine also favors the dissolution of crystals by decreasing supersaturation of uric acid (26).
The velocity of stone dissolution depends on the size and location of the stone and on flow of irrigation.
Furthermore, the microstructure of the stone, as observed at scanning electronic microscopy can influence the process of dissolution. In fact, stones that appeared macroscopically similar, may have major differences in microstructure by the presence of porosities, the distribution of organic matter and the size of crystals. The dissolution can be made difficult by the presence of shells of sodium/potassium urate or apatite as consequence of very high pH (above 7) and high uric acid concentration (27).

Combined treatment

The combination of alkalization with citrate and theobromine patented and commercialized by the company Devicare in its Lit-Control pH Up treatment (28, 29), allows to use lower doses of citrate, thus preventing excessive alkalinization to avoid formation of sodium urate crystals (30).
Furthermore, the reduced dose of potassium citrate administration decreases the risk of hyperkaliemia in patients with kidney failure or heart disease.

Theobromine and xanthinuria

Xanthinuria is a rare hereditary disorder related to a deficiency of *xanthine dehydrogenase/oxidase* (XDH/OX) causing an accumulation of hypoxanthine and xanthine due to a reduced degradation of these two precursors to uric acid. This results in hypouricemia, hypouricosuria, xanthinuria and formation of xanthine urinary stones (31, 32).
There are different types of xanthinuria due to mutations of different genes (33-35). The classical type I is caused by a mutation in XDH/XO gene mapped to chromosome 2p23.1. Type II depends on mutations in *molybdenum cofactor sulfurase gene* (MOCOS) localized on chromosome 18q12.2 that cause a defect of XDH/OX and *aldehyde oxidase* (AO). Triple deficiency of XDH, AOX and sulfite oxidase is caused by molybdenum cofactor deficiency type A (OMIM 252150) due to mutations in MOCS1 gene (6p21.1).
The classical presentation occurs at any age with renal colic, hematuria and urinary tract infection associated to xanthine stones. Less frequently the presentation is more severe with renal failure, muscle-skeletal and gastrointestinal symptoms. Traditional diagnosis with allopurinol loading test or liver biopsy has been replaced by genetic testing in stone patients with extremely low serum and low urinary uric acid replaced by xanthine.
The treatment for patients with xanthinuria is a low purine diet and high intake of fluids. In contrast to patients with uric acid stones, urine alkalinization is not effective because the solubility of xanthine is relatively independent of urinary pH.
A recent study showed that *1-methylxanthine* (1-MX), *7-methylxanthine* (7-MX), and *3-methylxanthine* (3-MX) significantly inhibited xanthine crystallization *in vitro* in a concentration dependent manner (36).

Two of these molecules are major metabolites of theobromine whereas the third is a metabolite of caffeine. In fact, after theobromine ingestion, 20% is excreted as theobromine, 21.5% as 3-MX, and 36% as 7-MX and after consumption of caffeine, 19% of it is excreted as 1-MX.
Hypoxanthine (HX), *theophylline* (TP), *paraxanthine* (PX), *theobromine* (TB), *caffeine* (CF), *1-methyluric acid* (1-MU), and *1,3-dimethyluric acid* (1,3-DMUA) showed no significant inhibitory effect on xanthine crystallization because only methyl derivatives of xanthine can be incorporated into the xanthine crystal lattice modifying its structure and slowing crystal growth (by increasing Gibbs free energy).
However, even if theobromine did not inhibit xanthine crystallization by itself, it could be used for prevention of xanthine stones by the effects of its metabolites.

Theobromine and gout

Gout is a rheumatic disease presenting with pain, swelling, and redness in the peripheral joints, especially in the metatarsophalangeal joint in the big toe and other joints in the feet and hands (37).
The disease is due to accumulation of *monosodium urate* (NaU) needle-shaped crystals in the affected joints. Synovial fluid is an ultrafiltrate from plasma with a pH of 7.4 and a sodium level of about 150 mmol/L. At a pH of 7.4 most uric acid is present as univalent anionic urate, whereas at serum urate level below 6 mg/dl sodium urate crystals do not form because sodium urate solubility threshold is 6.6 mg/dl. When urate levels are over the solubility limit of 6.6 mg/dl sodium urate crystals start to form. Furthermore, solubility of sodium urate is related to temperature and tends to decrease at temperature lower than 37°C, being only 3.7 mg/dl at 26°C. This explains why crystal formation is more common in the joints of the hands and feet where temperature tends to be lower (38).
The pathophysiology of crystal formation in synovial fluids is peculiar because the circulation of fluids in the cavities of synovial joints is quite limited with a much slower renewal of fluids compared to urinary tract where the flow of urine is continuous and relatively fast.
Consequently, inhibitors that can prevent crystal formation for a period up to 30-40 minutes can be useful in continuous flow of urine, but they are ineffective in absence of renewal of fluid as in the joint cavities.
Treatment of gout is based on anti-inflammatory drugs and the reduction of serum urate levels by a low purine diet, or drugs decreasing the production of uric acid, as allopurinol and febuxostat or drugs increasing the urinary excretion of uric acid, such as probenecid.
An alternative approach could be increasing urate solubility or inhibit sodium urate crystallization.
Some *in vitro* studies demonstrated that the combination of arginine-rich peptide and copper ions was able to delay the crystallization of sodium urate (39, 40). Similarly, the addition of trimethoprim to urate solutions delayed sodium urate crystallization because trimethoprim acted as competing binding agent forming a more soluble co-crystal with sodium urate (41).
Theobromine can form aggregates with uric acid through hydrogen bonds and aromatic stacking interactions (-stacking bonds) increasing urinary solubility of uric acid (42). Similarly, the solubility of uric acid increased in the presence of vitamin C (43). Furthermore, theobromine is also able to interact with uric acid crystals changing their morphology.
Epidemiological studies demonstrated that coffee and chocolate consumption decreased the risk of gout (44, 45).
An *in vitro* study suggested that 7-methylxanthine, a metabolite of theobromine, has the potential to be used for the prevention of gout (46). The same study found that 3-methylxanthine also prevented crystallization, although this happens at a four-fold-greater concentration than with 7-methylxanthine; 7-methyluric acid has a slightly stronger effect than 3-methylxanthine, but its plasma levels are negligible.
For this reason, consumption of 7-methylxanthine (or theobromine) has the potential for preventing the crystallization of sodium urate and the development of gout.
Regarding the safety of the treatment of 7-methylxanthine, studies documented that it has no toxic effects up to an oral dose of 1000 mg/kg of weight indicating that the consumption of 400 mg three times per day that should be requested to prevent gout seems to be safe.

Conclusions

Theobromine is a natural product that has several potential therapeutic applications. The use for the treatment of uric stones is the most promising because it allows the dissolution of uric acid stones faster with the use of lower doses of alkalizers. However, clinical efficacy must be confirmed by randomized clinical trials. Treatment with theobromine or its derivatives could be used in the treatment of xanthinuria or gout.

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