Effects on Uric Acid Metabolism of the Drugs except the Antihyperuricemics

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Abstract

A number of drugs commonly used in clinical practice can affect the serum concentration of uric acid. Some raise serum uric acid level by an increase in uric acid production or a decrease in uric acid excretion, while others lower serum uric acid level by an increase in uric acid excretion or decrease in uric acid absorption from intestine. In addition, salicylate shows so-called “biphasic effect”. At small doses it raises serum uric acid level, while at higher doses it lowers serum uric acid concentration. To understand the effects of those pharmacological agents on uric acid metabolism will help to avoid unexpected side effect of hyperuricemia and gout flare. In addition, hypouricemic property of some drugs may obviate the need for polypharmacy and improve the medication compliance.

Keywords: Pharmacological Agents; Hyperuricemia; Hypouricemia; Uric acid production; Uric acid excretion

Introduction

The normal adult male has a total body urate pool of approximately 1200 mg. Daily turnover of about 60 percent of the urate pool is achieved by balanced production and elimination of uric acid. About one-third of the human uric acid is derived from diet, while two-thirds is generated endogenously. The major site of purine synthesis is in the liver. The synthesis of uric acid occurs along two pathways, referred to as the de novo and the salvage pathways. Synthesis of the purine nucleotides begins with the formation of phosphoribosyl pyrophosphate (PRPP) by PRPP synthetase and leads to the first fully formed nucleotide, inosine 5’-monophosphate (IMP). IMP is converted into either adenosine 5’-monophosphate (AMP) or guanosine 5’-monophosphate (GMP) through two distinct reaction pathways. Catabolism of the purine nucleotides leads ultimately to the production of uric acid (Figure 1). On the other hand, about two-thirds of daily uric acid is excreted via the kidneys, and the remainder is excreted in feces. Many transport proteins are candidate participants in urate handling, with URAT1, GLUT9 and ABCG2 being the best characterized to date (Figure 2).

Drugs that Raise Serum Uric Acid Concentration

Decreased uric acid excretion

Decreased renal excretion of uric acid is the most common cause of hyperuricemia. Many drugs have been found to alter process of uric acid excretion and induce a rise in serum uric acid concentration.

![Figure 1: Purine metabolic pathway in humans.](image)

Abbreviations: ADA, adenosine deaminase; APRT, adenosine phosphoribosyltransferase; HPRT, hypoxanthine phosphoribosyltransferase; PNP, purine nucleoside phosphorylase; XDH, xanthine dehydrogenase

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Diuretics, pyrazinamide, nicotinamide, lactate, testosterone, and low dose salicylate are the representative drugs, which raise serum uric acid levels by a decrease in urinary uric acid excretion. Among them diuretic is probably the most common form of drug-induced hyperuricemia (Table 1).

**Diuretics**

Hyperuricemia is a relatively common finding in patients treated with loop diuretics and thiazide-type diuretics. It has been considered that diuretics raise serum uric acid concentration by decreasing circulating plasma volume. Diuretics reduce uric acid excretion by both directly and indirectly increasing uric acid reabsorption and decreasing uric acid secretion [2-4]. Recent studies on uric acid transporters revealed that multidrug resistance–associated protein 4 (MRP4), sodium-dependent phosphate transport protein 4 (NPT4), and organic anion transporters (OATs) are involved in the diuretics-induced hyperuricemia.

Loop diuretics are widely used to treat excessive fluid accumulation and edema of the body caused by cardiac failure, chronic kidney disease (CKD), and liver cirrhosis. Furosemide (20 mg, IV) decreased renal excretion and fractional clearance of uric acid when measured 1 to 2 hours after administration. Moreover, furosemide increased the plasma concentration of uric acid at 1.5 hours after administration [5]. Whether furosemide has any effect on URAT1 (SLC22A12) remains uncertain. Thiazides are usually considered not to affect serum uric acid level [12,13]. However, it has been reported that thiazides increase serum uric acid levels in the CKD patients [14], although the mechanism responsible for the increase in uric acid is unclear.

**Pyrazinamide and nicotinamide**

Pyrazinamide is an anti-tuberculous agent, and it increases serum uric acid level through decrease in uric acid excretion [15]. Pyrazinamide is usually administered as a two-month course during treatment of pulmonary tuberculosis, and hyperuricemia is reversible after withdrawal of the agent, therefore hyperuricemia due to pyrazinamide can be managed by observation and does not require withdrawal of the administration [16]. In the human kidney, uric acid is transported via URAT1 through the apical membrane of the proximal tubular cells, in exchange for organic anions, such as pyrazinoate, nicotinate, and lactate transported towards the tubular lumen. It has been reported that pyrazinamide reduces the renal secretion of uric acid via activation of the exchange transport of uric acid with pyrazinecarboxylic acid, which is a metabolite of pyrazinamide, through the uric acid transporter URAT1 [17,18]. Moreover, hOAT10-mediated 14C-urate uptake was elevated by an exchange with L-lactate, pyrazinoate, and nicotinate [19]. Ethambutol, another anti-tuberculous agent, also produces an increased serum concentration of uric acid in about 50% of patients, due to decreased renal excretion [20]. The mechanism of increased serum concentration of uric acid by ethambutol administration is not clear, though seems to differ from that of pyrazinamide and diuretics.

Nicotinic acid has been used to treat dyslipidemia. Nicotinic acid decreases the concentrations of both very-low-density lipoproteins (VLDL) and plasma triglyceride (TG), besides elevating HDL cholesterol. Elevated blood levels of uric acid have been noted with nicotinic acid therapy [21]. Uric acid raising effects of nicotinic acid may occur when the drug is given in therapeutic doses of 1,500 mg

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### Table 1: Drugs that raise serum uric acid.

| Diuretics (loop and thiazide types) | Filgrastim (Granfilgrastim) |
|-----------------------------------|---------------------------|
| b-blockers                         | Rivaroxaban, Inferon |
| Low dose aspirin                   | Ronitrol (Novoral) |
| Pyrazinamide, Ethambutol           | Darunavir (Prezista) |
| Nicotinic acid, Niacin              | Didanosine (Videx) |
| Lactic acid                        | Ritonavir (Ritonavir) |
| Cyclosporin, Neoral, Sandimmune    | Basaliximab (Simulect) |
| Tacrolimus, Prograf                | Teriparatide (Forteo) |
| Fructose, Xylitol, Theophylline    | Sildenafil (Viagra, Revatio) |
| Levodopa, Sinemet                  | Diazoxide (Arloglycem) |
| Cytotoxic agents                   |                          |

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daily or doses of up to six grams. However, nictoritrol, a niacin derivative, for 5 months’ administration of 750 mg/day seems to have no detrimental influence on serum uric acid concentration [22]. In addition to URAT1 mediated nicotinate exchanging for uric acid reabsorption, OAT 10 mediated uric acid uptake is also facilitated by exchange with nicotinate, suggesting the molecular evidence of nicotinate-induced hyperuricemia [19].

Lactate

Lactated Ringer’s injection, has similar osmolarity to body fluids, is indicated as a source of water and electrolytes or as an alkalinizing agent. High dose lactate infusion (0.17-0.2 mol) leads to an increase in serum uric acid with a decrease in uric acid clearance [23,24]. However, lactate content in the high caloric solution (Flucaliq™) is 3.723 g/L, and high dose and long term administration of lactate is clinically rare, the effect of lactate infusion on the serum uric acid level may not be clinically important. During lactate is secreted through URAT1, uric acid is reabsorbed by exchange, causing an elevation of serum uric acid level. In addition to URAT1 mediated lactate exchanging for uric acid reabsorption, OAT 10 mediated uric acid uptake is also facilitated by exchange with lactate, suggesting the molecular evidence of lactate-induced hyperuricemia [19].

Cyclosporine

Cyclosporine A is used as a common immunosuppressant for management of organ transplantation and various autoimmune diseases. Cyclosporin A increases serum uric acid level by renal damage and/or decreased uric acid excretion. Although hyperuricemia is a well-known adverse effect of cyclosporine, tacrolimus also increases serum uric acid level [25]. On the contrary, azathioprine seems not to affect serum uric acid level. Recently it is revealed that cyclosporine A enhanced uric acid uptake through OAT10, providing molecular evidence for cyclosporine A-induced hyperuricemia [19]. Cyclosporine-induced hyperuricemia is mitigated by concomitant administration of amloidipine or losartan [26,27].

Testosterone

Serum uric acid level of man is higher than that of woman, which is attributed to androgen-induced uric acid reabsorptive transport system in the kidney. According to a study using orchietomized mice model, testosterone replacement enhanced mRNA and protein levels of sodium-coupled monocarboxylate transporter (SMCT1), while enhanced mRNA of URAT1, suggesting the induction of SMCT1 by testosterone is a candidate mechanism underlying hyperuricemia in males [28]. Testosterone replacement therapy against females with gender identity disorder increased serum uric acid level, and a positive correlation between increased levels of serum uric acid and serum creatinine. Thus it may be considered that testosterone-induced hyperuricemia is at least partially attributed to an increase in muscle mass, a major source of purine [29], although uric acid production is not estimated.

Increased Uric Acid Overproduction

Uric acid is produced by decomposition and catabolism of purine nucleotides, and external ingestion of purine body. It is endogenously produced by degradation of ATP or increased turnover rate of cell death. The diminution of ATP and the resulting elevation of AMP and IMP levels appear to trigger activation of purine nucleotide degradation. Certain drugs, such as fructose, xylitol, and theophylline can increase uric acid levels in the blood by accelerated purine nucleotide degradation, while certain cytotoxic agents increase uric acid production by an increased turnover rate of cell death.

Fructose

Fructose is widely used intravenously as a carbohydrate nutrient. Fructose infusion is indicated in patients requiring fluid replacement and caloric feeding. It is metabolized more rapidly than dextrose without requiring insulin and thus is used in diabetic patients. It is significantly metabolized to fructose-1-phosphate by fructokinase with an abrupt consumption of adenosine triphosphate (ATP) and phosphate, and increased activity of AMP deaminase suppressed by phosphate, consequently, degradation of adenosinenucleotide is accelerated, hence increasing the synthesis of uric acid [30]. Fructose also inhibits the excretion of uric acid, apparently by competing with uric acid for access to the transport protein GLUT 9 [31]. Fructose (1.0 g/kg) administration increased the plasma concentration of uric acid, together with an increase in the plasma concentration of oxypurines, supporting that an increase in the plasma concentration of uric acid is ascribable to increased purine degradation [32]. On the contrary, 10% intravenous fructose (0.5 g, per kg, body-weight per hour) did not appreciably change serum uric acid level, it is suggested that the hyperuricemic effect of fructose previously reported is dose-related and associated only with larger than physiological concentrations of fructose infused under experimental conditions [33]. Fructose should be infused at a speed below 0.5 g/kg/hour to avoid a rise in uric acid level.

Xylitol

Xylitol has been suggested as a more advantageous calorie source for intravenous administration than glucose in certain clinical situations. Xylitol injection is indicated as the sugar substitutes for diabetics. However, xylitol increases uric acid levels particularly if higher doses are administered, as 0.25 g/kg/hour (1000 ml 10% fructose) did not appreciably change serum uric acid level, xylitol (up to 6 g) administration increased the plasma concentration of uric acid, together with an increase in the plasma concentration of oxypurines, supporting that an increase in the plasma concentration of uric acid is ascribable to increased purine degradation [34]. On the contrary, xylitol injection is indicated as the calorie substitute for diabetics and as a more advantageous calorie source for intravenous administration than glucose in certain clinical situations. Xylitol injection is indicated as the sugar substitutes for diabetics. However, xylitol increases uric acid levels particularly if higher doses are administered, as 0.25 g/kg/hour (1000 ml 10% fructose) did not appreciably change serum uric acid level, xylitol (up to 6 g) administration increased the plasma concentration of uric acid, together with an increase in the plasma concentration of oxypurines, supporting that an increase in the plasma concentration of uric acid is ascribable to increased purine degradation [34]. On the contrary, xylitol injection is indicated as the calorie substitute for diabetics.
xylitol at a rate of 0.25 g/kg/hour or faster is not safe [34]. Xylitol is first oxidized to D-xylulose by the NAD-xylitol dehydrogenase, causing the NADH/NAD ratio to increase. The next step is the phosphorylation of D-xylulose to D-xylulose-5-phosphate by D-xylulose-kinase, causing ATP and inorganic phosphate consumption. As a consequence, adeninenucleotide degradation is accelerated, resulting in buildup of serum uric acid level (Figure 4). Xylitol should be infused at a speed below 0.3 g/kg/hour to avoid a rise in uric acid level.

Theophylline

Theophylline, a methylxanthine drug, is used for respiratory diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD) to prevent and treat symptoms including wheezing, shortness of breath, and chest tightness. The pharmacological actions of theophylline include bronchial smooth muscle dilatation, increased heart muscle contraction and renal blood flow, and anti-inflammatory effects. Serum uric acid concentration of the patients with asthma taking theophylline is higher than that not taking theophylline, and serum uric acid increases with serum theophylline concentrations [35]. Theophylline increased the plasma concentrations of purine bases (uric acid, hypoxanthine and xanthine) without a decreased urinary excretion of these purine bases in normal subjects. 1-methyl uric acid, a metabolite of theophylline, was not converted to uric acid, which suggested that theophylline-induced purine degradation seems to be a cause of the increased concentration of uric acid in plasma, although theophylline affected neither the concentration of nucleotides nor the activities of the enzymes related to purine metabolism (hypoxanthine-guanine phosphoribosyl transferase, 5’-nucleotidase, adenosine deaminase and purine nucleoside phosphorylase [36].

Cytotoxic agents

Some cytotoxic agents, such as anthracyclines and doxorubicin derivatives cause raised levels of uric acid in the blood by renal damage and/or increased turnover rate of cell death. The extreme case of massive tumor cell lysis is named as tumor lysis syndrome, which damage and/or increased turnover rate of cell death. The extreme case of massive tumor cell lysis is named as tumor lysis syndrome, which is clinically not problematic and is considered to be rather preferable effect except for renal toxicity (Table 2).

Increased Uric Acid Excretion

Estrogen

Serum uric acid concentration of adult women is lower than in men of a similar age. Menopause is associated with higher serum uric acid levels and post-menopausal estrogen replacement decreases serum uric acid concentration [38]. The underlying mechanism is considered to be related to an increased renal clearance of uric acid in women, possibly due to their higher plasma estrogen levels [39,40]. Little has been known why estrogen increases renal uric acid excretion. However, recently it has been revealed that estradiol suppressed the protein levels of URAT1 and Glut9 [41].

Antihypertensives (Sartans, calcium channel blockers)

Effect of antihypertensives on uric acid metabolism differs from class to class. As mentioned above, diuretics raise serum uric acid, and β blockers also raise serum uric acid level. Calcium antagonists increase uric acid clearance by increasing glomerular filtration. Effect of calcium

Drugs that Lower Serum Uric Acid Concentration

Drugs with hypouricemic properties, not primarily intended for the treatment of hyperuricemia include acetohexamide, azauridine, chlorprothixene, dicumarol, estrogens, fenofibrate, glycerol guaiacolate, iopanoic acid, losartan, meglumine iodapamide, phenylbutazone, salicylates and other NSAIDs, sodium diatrizoate, trimetropim-sulfamethoxazole, and contrast media. Most known of which are estrogen, fenofibrate, and losartan. Decreased serum level of uric acid by drugs is mostly attributable to their uricosuric action, which is clinically not problematic and is considered to be rather preferable effect except for renal toxicity (Table 2).

Table 2: Drugs that lower serum uric acid.

| Drugs                          | Effect                                    |
|-------------------------------|-------------------------------------------|
| Acetohexamide (Dimelin®)       | Azauridine                                |
| Dicoumarol                    | Iopanoic acid                             |
| Iopanoic acid                 | Meglumine iodapamide                      |
| Phenylbutazone                | Calcitonin                                |
| Kremezin                      | Sevelamer (Phosblock®)                    |
| Levotofospan                  | Tranlast (Rizaben®)                       |
| o,p′-DDD (Operepin®)          |                                          |

Figure 4: Adeninenucleotide degradation associated with xylitol metabolism.
channel blockers and angiotensin converting enzyme (ACE)-inhibitors on serum uric acid level is controversial; some describe the uric acid lowering effect and others do not. Intravenous infusion of diltiazem has uricosuric and hypouricemic effects in rats, possibly due to an increase in glomerular filtration rate [42]. Neither serum uric acid nor clearance and fractional excretion of uric acid changed significantly during 10-day treatment with nifedipine [43], while recent evidence suggested nifedipine has been found to reduce serum uric acid levels compared with a placebo in the A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) trial [44]. Furthermore, it has been suggested that amlodipine and cilnidipine might reduce serum uric acid level [45,46]. Captopril and enalapril increased uric acid excretion, and captopril significantly reduced serum uric acid in hypertensive patients with hyperuricemia [47], while it has been reported that ACE-inhibitors have not been associated with lower serum uric levels [48,49].

Angiotensin II receptor blocker (ARB), losartan increased excretion of uric acid and decreased the serum uric acid level in both healthy and hypertensive subjects [50-52]. After 100 mg administration of losartan, plasma concentrations of uric acid decreased by 8% and 16%, at 1.5 and 2.5 hour, respectively. Urinary excretion of uric acid increased by 3.9-fold and 2.6-fold, at 1 to 2 hour and at 2 to 3 hour, respectively, while the fractional clearance of uric acid was increased by 4.3- and 3.2-fold at 1 to 2 hour and at 2 to 3 hour, respectively [53]. Therefore, losartan might be a useful therapeutic tool to control blood pressure and reduce serum uric acid levels in hypertensive patients with hyperuricemia and/or gout. The uricosuric action of losartan is exerted by its inhibition of URAT1 expressed in the brush-border membrane of the renal proximal tubules [54,55]. Other ARBs have not been considered to affect serum uric acid level [56-58]. Thus, the effects of various ARBs on the disposition of uric acid might be different.

Data from Losartan Intervention For End point Reduction In Hypertension (LIFE) study suggest treatment-induced decrease in serum uric acid may contribute to the treatment benefit of a losartan-based versus atenolol-based therapy on the composite endpoint (death, myocardial infarction, or stroke) [59]. According to a large case-control study exploring the effect of antihypertensive drugs on the risk of incident gout attacks, calcium channel blockers and losartan are associated with a lower risk of incident gout among people with hypertension. By contrast, diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout [60].

**Fenofibrate**

It has been shown that fenofibrate, a hypolipidemic fibrac acid derivative decreases serum uric acid by 20% [61]. In hyperlipidemic patients, fenofibrate (300 mg/day) for 12 weeks decreased serum uric acid concentration by 36% and increased fractional uric acid clearance by 62% [62]. Three days’ administration of fenofibrate 450 mg increased fractional clearance of uric acid, compared to baseline value, while the plasma concentration decreased in normal subjects [63]. Mechanism by which fenofibrate decreases serum uric acid levels by increasing its urinary excretion is considered to be the inhibition of URAT1 by fenofibric acid, major metabolite of fenofibrate [64]. An in vitro study using HEK 293 cells expressing URAT1 showed IC50 of fenofibric acid is reported to be 35.68 ± 3.94 μM (benzbromarone, 0.13 ± 0.01 mM) [64].

**Statins**

Statins are competitive inhibitors of the enzyme HMG-CoA reductase, and are used for the treatment of high LDL-cholesterol. Atorvastatin and rosuvastatin decrease serum uric acid levels, respectively, but pitavastatin dose not [65]. High dose atorvastatin (40 mg/day) significantly decreased serum uric acid levels although the underlying mechanisms remain speculative [66]. Rosuvastatin (10 mg/day) exhibits a similar uric acid-lowering effect [67].

**Decreased uric acid absorption**

Drugs that lower serum uric acid by decreased production have not been described except xanthine oxidase inhibitors, which are widely used for hyperuricemia/gout. Sevelamer, a nonabsorbed hydrogel that binds phosphorus and bile acids in the intestine, and used to treat hyperphosphatemia in CKD patients on hemodialysis, decreases serum uric acid concentration, possibly by adsorbing uric acid [68,69]. The reduction has not considered detrimental effect, rather a beneficial one.

**Drug that Raises or Lowers Serum Uric Acid According to its Doses (paradoxical effect)**

**Salicylate**

Salicylic acid and its derivatives are the most prescribed analgesic, antipyretic, and anti-inflammatory agents. Salicylates have a “paradoxical effect” on the handling of uric acid by the kidney. The action of salicylates on uric acid excretion depends on the dose of salicylates. At doses of less than 2.5 g/day, salicylates cause the retention of uric acid by blocking the tubular secretion of uric acid, while at dose of higher than 3 g/day, they cause increased urinary excretion of uric acid [70]. Mini-dose aspirin, even at a dosage of 75 mg/day, caused a decrease in uric acid excretion and raised serum uric acid level [71]. It has been suggested that the “paradoxical effect” of salicylate can be explained by two modes of salicylate interaction with URAT1: (1) acting as an exchange substrate to facilitate uric acid reabsorption, and (2) acting as an inhibitor for uric acid reabsorption [72]. Low dose of salicylate interact with OAT1/OAT3, the uric acid secreters [73].

**Effects of various drugs on uric acid transporters are indicated in Figure 2**

**Others:** High-dose trimethoprim-sulfamethoxazole is associated with a reduction in serum uric acid concentration [74]. Chlorprothixene, a major tranquilizer shows strong uricosuric action and lowers serum uric acid, which may be used as an indicator of treatment compliance [75]. Zuclophenthicol, an antipsychotic drug of the thioxanthene class, is also a potent uricosuric agent, thus capable of producing persistent hypouricemia [76].

Tranilast, an anti-allergy drug originally developed in Japan, decreases serum uric acid level by increased urinary excretion. Tranilast can inhibit uric acid transport through both GLUT9 and URAT1 proteins, with an IC50 (approximately 16 mM and 24 μM, respectively) consistent in each case with the level of exposure in humans resulting from doses that produce a uricosuric effect. This suggests that the uricosuric activity of tranilast is due to inhibition of these reabsorptive urate transporters in the kidney [77].

Levotofisopam is the S-entantiomer of the racemic mixture RS-tofisopam, a nonseading agent used for the treatment of a variety of disorders associated with stress or autonomic instability. Tofisopam decreases serum uric acid level by increasing uric acid excretion (submitted). However, the target uric acid transporter of tofisopam remains to be clarified.
It has been reported that administration of cilostazol 200 mg for 12 weeks decreased serum uric acid, although the mechanism is not clear [78].

Hypouricemic effects of glyceryl guaiacolate, an expectorant and o,p’-DDD, an antineoplastic drug used to treat adenocortical carcinoma by increased uric acid clearance have been reported [79,80].

Choi et al. showed that people with a higher vitamin C intake have a lower risk of gout [81]. There is also a study in healthy volunteers that suggests that supplementation with 500 mg/day of vitamin C for 2 months reduces serum uric acid levels [82]. Although the precise mechanism is unknown, it is considered that vitamin C increases the uric acid excretion [83-86]. However, a latest research revealed that modest dose of vitamin C (500 mg/day) for 8 weeks does not reduce uric acid level to a clinically significant degree in patients with gout [87].

Conclusion

To understand the effects of pharmacological agents on uric acid metabolism will help to avoid unexpected side effect of hyperuricemia and gout flare. In addition, availng hypouricemic property of some drugs, pleiotropic effects (antihypertensive-hyypuricemic or antilipidemic-hyypuricemic actions) and/or improvement of the metabolism will help to avoid unexpected side effect of hyperuricemia [87].

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