Pharmacological Review on Uricosuric activity

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Abstract
The naturally available uricosuric agents are Tinospora cardifolia, Allium sepa, Cajanus Cajan, Piper nigrum etc., Natural medicinal plants having no side effects are more preferred when compared to synthetic medications. Uricosuric agents increase the urinary excretion of uric acid hence the natural uricosuric agent is preferred to prevent many diseases like gout, arthritis, kidney stones etc., without side effect. Uricosuric medications are the substances that increase the excretion of uric acid in urine, thus reducing the concentration of uric acid in blood plasma. Prolonged and untreated hyperuricemia results into gout, a severe inflammatory condition. Sustain hyperuricemia leads to impaired blood pressure control, renal impairment and nephropathy. The common factors for deposition of uric acid in blood are drinking alcohol and taking high purine diet. The various screening methods for the uricosuric activity are uricosuric activity in mice, Potassium oxonate induced activity, and Phenol red excretion methods are explained in this review.

Introduction

Uricosuric medications are the substances that increase the excretion of uric acid in urine, thus they reduce the concentration of uric acid in blood plasma. Prolonged and untreated hyperuricemia results into gout, a severe inflammatory condition. Sustain hyperuricemia leads to impaired blood pressure control, renal impairment and nephropathy. The drugs used in treatment of hyperuricemia and for prophylaxis of gout include xanthine oxidase inhibitors like allopurinol and uricosuric agents like probenecid and benz bromarone. Allopurinol is contraindicated in patients with compromised renal function and frequently causes severe hypersensitivity reactions. Febuxostat is contraindicated in liver failure. Uricosuric agents furthermore can’t be administered in patients with renal stones. So, it is the need of the today to find out novel drug with minimal adverse effects.

Uricosurics

The Uricosuric medications are defined as the substances that increase the excretion of uric acid in urine. Thus they reduce the concentration of uric acid in the blood plasma. All drugs that reduce blood uric acid are not uricosurics there is another different mechanism to reduce blood uric acid concentration by anti-gout medications. Uricosurics are often used in the treatment of gout.

Uricosuric drugs which increase the urinary excretion of uric acid, or XO inhibitors which block the terminal step in uric acid biosynthesis, can lower the plasma uric acid concentration, and are generally employed for the treatment of gout. Allopurinol is a clinically used Xanthine oxidase inhibitor in the treatment of gout, but this drug suffers from many side effects such as hepatitis, nephropathy and allergic reactions. Moreover allopurinol and its active metabolite oxypurinol is catalyzed by Xanthine oxidase itself, resulting in the generation of reactive oxygen species such as Superoxide anion (O2-) is involved in various pathological states such as hepatitis, inflammation, ischemia, reperfusion, carcinogenesis and aging.

Etiology for deposition of Urac acid
The common factors involved in deposition of uric acid in the blood plasma are

- Drinking alcohol
- High purine alcoholic beverages such as beer
- Taking sea food and meat in diet constantly
- Medical conditions like diabetes, obesity, high blood pressure

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All these above factors are involved in the formation of uric acid in the blood plasma.

**Classification of Uricosuric Drugs**

The uricosuric drugs are classified into the following two types:

1. Primary uricosurics
2. Secondary uricosurics
   
   1. Primary Uricosurics: The primary uricosuric drugs include
      - Probenecid
      - Benz bromarone
      - Sulfinpyrazone
   
   2. Secondary Uricosurics: Drugs with other primary uses and also having the properties of uricosuric drugs are known as secondary uricosurics.
      - Amlodipine
      - Atorvastatin
      - Fenofibrate
      - Losartan
      - Adrenocorticotropic hormone
      - Cortisone

**Mechanism of action of Uricosuric drugs**

The general mechanism of action of uricosuric drugs is explained as follows:

- Uricosuric drugs acts primarily on the proximal tubules in the kidney.
- They interfere with the absorption of uric acid from the kidney back into the blood.
- Uricosurics act by blocking the function of a protein encoded by gene SLC22A12. It is also known as urate transporter 1 or URAT 1.
- URAT 1 acts as a central mediator in the transport of uric acid from kidneys into the blood.
- Thus the uricosuric drugs reduce the concentration of uric acid in the blood.

**Diagnosis Tests for Determination of Uric Acid**

The various diagnostic tests involved in the determination of uric acid in the blood and urine primarily depends on the chemical or enzymatic oxidation to allantoin. The various diagnostic tests are:

- Manual colorimetric method
- Automated colorimetric method
- Manual enzymatic methods
- Automated enzymatic methods
- Chromatographic determination of uric acid and related purines
- Colorimetric titration.

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**Figure 1:** This figure describes the mechanism of action of uricosuric medications like probenecid.
Uricosuric activity

Synthesis of uric acid primarily occurs in the liver, but the kidney has an important role in the patho-physiology of hyperuricemic syndromes. Because uric acid is poorly soluble, excessive amounts in the circulation may precipitate out into the tissues, particularly the joints, resulting in a painful arthropathy (“Gout”). In humans these condition is usually the result of faulty tubular transport of urate, resulting in increased net reabsorption.

Reduction of net uric acid synthesis by inhibition of xanthene oxidase is the preferred therapeutic approach. Xanthine oxidase catalyzes the oxidation of hypoxanthine and xanthene to uric acid.

Methods for determining the uricosuric activity

The following methods were used to determine the uricosuric activity on animal models.

1. Uricosuric activity in mice.
2. Uricosuric activity after Potassium Oxonate treatment in rats.
3. Phenol red excretion in rats.

Uricosuric activity in mice

Procedure

1. Male NMRI mice weighing 25-30g are used.
2. On the evening prior to the experiment, food but not water is withheld.
3. In the morning, the mice are orally loaded with 50ml/kg 0.9% Nacl solution.
4. Together with the sodium load the test compound is applied by gavage in 2% starch suspension. Controls receive saline and starch suspension only.
5. Groups of 5 mice are placed into metabolic cages.
6. Urine is collected over 4h. In the urine sodium and potassium are determined by flame photometry, chloride by argentometrically with potentiometrical end point titration (Chloride titrator, Aminco). Uric acid is determined by the Uriquant-method.
7. Creatinine is determined by the jaffe-reaction.

Uricosuric activity after potassium oxonate treatment in Rats

Procedure

1. Male Wistar rats weighing 250g are placed individually in metabolic cages.
2. They are offered a special diet containing 5% fructose, 3% Uric acid, 2% potassium oxonate (2,4-dihydroxy-1,3-triazine-6-carboxonic acid) and 0.001% artificial sweetener.
3. Drinking water consists of a 0.5% solution of potassium oxonate solution.
4. The treatment is repeated on the second day.
5. On the third day 24 h urine is collected and the animals are sacrificed by exsanguinations.
6. Concentrations of uric acid and electrolytes (Na⁺, K⁺, and Cl⁻) are determined in blood and urine.

Phenol red excretion in Rats

Procedure

1. Phenol red (phenolsulphonphthalein) excretion is an indirect test for uricosuric activity.
2. Male Wistar rats weighing 120-150g are treated orally with the test compound or the standard compound.
3. 30min prior to intravenous injection via the tail vein with 2.5ml/kg of a 3% aqueous solution of phenolsulfonphthalein for intravenous application, 5.0 ml/kg of the test drug solution are injected immediately after the phenolsulfonphthalein injection followed by flushing with 2.5ml/kg saline.
4. By retro-orbital puncture blood samples are withdrawn after 30, 60 and 180 min.
5. Blood (0.2ml) is diluted with 2ml 0.9% Nacl- solution and centrifuged.
6. To 1ml of the supernatant 1 ml of 1% sodium carbonate solution and 8 ml of saline are added.
7. Using spectrophotometer extinction at 546 nm is determined.

Plants with uricosuric activity

Table 1: Shows plants having Uricosuric activity

| S.No | Medicinal Plant Name | Part Used | Other Uses                        |
|------|----------------------|-----------|-----------------------------------|
| 1.   | *Tinospora cardifolia* | Leaf      | Diabetes, Hepatitis               |
| 2.   | *Allium sepa*        | Bulb      | Hay fever, cold and cough         |
| 3.   | *Barleria prionitis* | Root      | Respiratory diseases, joint pains |
| 4.   | *Bauhinia variegate* | Flower    | Astringent, dysentery             |
| 5.   | *Brassica nigra*     | Seed oil  | Condiment, lubricant              |
| 6.   | *Cajanus cajan*      | Seed      | Diabetes, food poisoning, constipation |
| 7.   | *Calamus rotang*     | Stem bark | Chronic fever, antidote to snake venom |
| 8.   | *Cassia senna*       | Leaf, fruit | Laxative, constipation            |
The above table 1 describes about the medicinal plants with uricosuric activity and the other uses of the medicinal plants. These table can be taken as reference for further research on uricosuric activity.

**Conclusion**

I would likely to take this time to summarize everything i have said in this blog regarding uricosuric activity. Uricosuric agents increase the excretion of uric acid thus reducing the concentration of uric acid in the body and increasing its rate of elimination. The medicinal plants having uricosuric activity and the screening models for uricosuric activity are explained in this activity. Therefore natural medicinal plants having no side effects are more preferred when compared to synthetic medications.

**References**

1. Feig DI, Mazzali M, Kang DH, Nakagawa T, Price K, Kannelis J, Johnson RJ. Serum uric acid: A risk factor and a target for treatment? J Am Soc Nephrol. 2006; 17: S6 73.
2. Chohan S, Becker MA. Update on emerging urate-lowering therapies. Curr Opin Rheumatol. 2009; 21: 143-49.
3. Perez-Ruiz F, Hernando I, Villar I, Nolla JM. Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels:

Another insight to allopurinol-related toxicity. J Clin Rheumatol. 2005; 11: 129- 33.

4. Halevy S, Ghislain PD, Mockenhaupt M, Fogat JP, Bouwes Bavinck NJ, Sidoroff A, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008; 58: 25-32.
5. Rider TG, Jordan KM. The modern management of gout. Rheumatology (Oxford). 2010; 49: 5-14.
6. Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ, Herrero- Beites A, Ruiz-Lucea E, Garcia-Erauskin G, Duruelo J, and Alonso-Ruiz A. Treatment of chronic gout in patients with renal function impairment: An open, randomized, actively controlled study. J Clin Rheumatol. 1999; 5: 49-55.
7. Terkeltaub R.Gout. Novel therapies for treatment of gout and hyperuricemia. Arthritis Res Ther 2009; 11:236.
8. Osada Y, Tsuchimoto M, Fukushima H, Takahashi K, Kondo S, Hasegawa M, Komoriya K.Hypouricemic effect of the novel Xanthine oxidase inhibitor,. TEI-6720, in rodents. Euro J Pharmacology 1993; 241:183-188.
9. Akaife T, Maeda H. Pathophysiological effects of high-output production of nitric oxide. In: Ignarro LJ, ed. San Diego: Academic Press: 2000; P733–45.
10. Cos P, Ying L, Calomme M, Hu JP, Cimanga K, Van Poel B, Pieters L, Vlie tinck AJ, Berghe DV. Structure-activity relationship and classification of flavanoids as inhibitors of Xanthine oxidase and superoxide scavengers. J Nat Prod 1998; 61:71-76.
11. Diamond, HS, Meisel, A, Sharon, E, Holden, D, and Catatian, A: Hyperuricosuria and increased tubular secretion of urate in sickle cell anemia. Amer J Med 1975;59:796.
12. Hamada T, Ichida K, Hosoyamada M, Mizuta E, Yanagihara K, Sonoyama K, Sugihara S, Igawa O,
Hosoya T, Ohtahara A, Shigamasa C, Yamamoto Y, Ninomiya H, Hisatome I. "Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients". Am. J. Hypertens.; 2008; 21 (10):1157-62.

13. R W. E. WATTS M.R.C. Clinical Research Centre, Harrow, Middlesex Determination of Uric Acid in Blood and in Urine Ann. din. Biochem. 1974; 11:103.

14. Shinosaki T, Yonetani Y. Hyperuricemia induced by the uricosuric drug probenecid in rats. Jpn J Pharmacol. 1991;55: 461-468.

15. Fanelli GM (1976) Drugs affecting the renal handling of uric acid. In: Martinez-Maldonado M (ed) Methods in pharmacology Vol 4A: Renal Pharmacology Chapter 9, pp 269-292, Plenum Press, New York and London.

16. Dan T, Yoneya T, Onuma E, Ozawa K. Hypouricemic and Uricosuric actions of AA-193 in a hyper-uricemic rat model. Metabolism 1994;43:123-128.

17. Turner RA (1965) Uricosuric agents In: Screening Methods in Pharmacology Chapter 39, pp 262-263, Academic press, New York and London.

18. Dr. K. Madhava chetty, K. Sivaji, K. Tulasii Rao. Flowering plants of chittor district Andhra Pradesh, India. Page No: 550.