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Pre-Clinical Investigation of the Effect of Xanthine Oxidase Inhibitors on the Bioavailability of 6 Mercaptopurine

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Abstract

6 Mercaptopurine (6MP) is extensively utilized in oncology and inflammatory disorders such as acute lymphoblastic leukemia (ALL) and inflammatory bowel disease (IBD). Xanthine oxidase inhibitors (allopurinol and febuxostat), utilized as first-line treatments for hyperuricemia, may affect the absorption of 6-mercaptopurine (6MP). This study aims to assess the impact of allopurinol and febuxostat on the oral bioavailability of 6-mercaptopurine (MP). Allopurinol and febuxostat were evaluated for their effects on the plasma levels of 6MP. Three cohorts of healthy rabbits were assigned to an experimental protocol involving varying dosages of 6MP: 10 mg/kg, 20 mg/kg allopurinol, and 30 mg/kg febuxostat. The hematological data indicate that allopurinol pretreatment markedly enhances 6MP bioavailability, necessitating meticulous dosage modifications. Administering 6MP alongside XOIs necessitates a substantial reduction in dosage, typically to one-third of the standard level, to prevent severe adverse effects. To guarantee patient safety and therapeutic effectiveness, stringent monitoring and personalized dosages are essential.

Keywords: Xanthine Oxidase (XO) Inhibitors, 6-mercaptopurine (MP), Bioavailability, Safety

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Introduction

Xanthine Oxidase (XO) Inhibitors are widely used for hyperuricemia and gout (Chinchilla *et al*., 2016; Alghamdi *et al*., 2021). Hyperuricemia is directly linked to impaired uric acid excretion or elevated intake of purine-rich foods (Benn *et al*., 2018; Danve *et al*., 2021). Three primary strategies are employed in the management of hyperuricemia and its associated symptoms: first, restricting the intake of purine-rich foods, which is frequently effective for borderline, asymptomatic hyperuricemia; second, the administration of therapeutic agents that inhibit the xanthine oxidase (XO) enzyme; and third, the use of therapeutic agents that promote the excretion of uric acid (Khanna *et al*., 2014; Chinchilla *et al*., 2016; Li *et al*., 2016). In addition to, now Febuxostat a non purine, selective and non-competitive inhibitor of XO is also available and (Grewal *et al*., 2014) it is more effective in comparison to allopurinol (Stockert & Stechschulte, 2010).

Moreover, XO inhibitors play a significant role in the metabolism of thiopurine drugs. 6 mercaptopurine (6MP), a cytotoxic purine analog frequently utilized in leukemia treatment, is expected to be influenced by the XO inhibitors (Sandborn, 2010; Schmiegelow *et al*., 2014). Owing to significant first-pass metabolism in the liver and intestines, 6MP has markedly restricted oral bioavailability. Production of inactive 6 Thiouric acid (6TU), hepatotoxic Methyl Mercaptopurine (MMP) nucleotides, and pharmacologically active 6 Thioguanine (6TGN) nucleotides, utilizing the enzymes Xanthine oxidase (XO), thiopurine methyltransferase (TPMT), and hypoxanthine phosphoribosyl transferase (HPRT), respectively (Chouchana *et al*., 2013).

When providing 6MP, the concomitant use of xanthine oxidase inhibitors, such as allopurinol and febuxostat, reduces serum urate levels by obstructing the function of xanthine oxidase (Harahap *et al*., 2022; Machate *et al*., 2022; Iftode *et al*., 2024; Rivera & Carter,

2024). The inhibition of XO results in less first-pass metabolism and increased bioavailability of 6MP, facilitating a larger fraction of 6MP to be converted into therapeutically active 6TGN metabolites, which are incorporated into DNA, leading to base mispairing and DNA strand breakage (Schmiegelow *et al*., 2014).

The co-prescription of allopurinol and 6-mercaptopurine is employed to enhance pharmacological treatment in individuals with inflammatory bowel disease (IBD) (Seinen *et al*., 2016). This interaction is relevant for certain patients with inflammatory bowel disease (IBD) who exhibit inadequate response or resistance to 6-mercaptopurine (6MP) because of its reduced bioavailability. Allopurinol was originally developed to enhance the efficacy of 6-mercaptopurine in patients with acute leukemia, increasing Allopurinol bioavailability up to fivefold (Stockert & Stechschulte, 2010; Doré *et al*., 2014). Other studies have also reported that the interaction of 6MP with the XO inhibitor leads to myelotoxicity (Gardiner *et al*., 2011). Keeping in view this critical issue, the current study aims to assess the impact of the use of allopurinol and febuxostat on the in vivo oral bioavailability of 6MP (Juhari *et al*., 2023; Muresan *et al*., 2023; Kilroy *et al*., 2024; Zar *et al*., 2024).

Materials and Methods

The study required mainly three chemicals, among which Allopurinol (CAS: 315-30-0), 6 MP (CAS: 6112-76-1), and febuxostat (CAS: 144060-53-7) were purchased from Sigma-Aldrich. Rabbits were selected as the experimental subjects from the university animal house. The assay protocol was in line with the pre-published literature that has published and explored the technicalities and assay protocols for the 6MP (Chowdhary *et al*., 2013; Somasekhar, 2014).

Preparation of Stock Solution & Standard Curve

Only a 0.1N solution of NaOH was made, for which 4g of NaOH was placed into 1000ml volumetric flask and diluted to the mark with distilled water; 6 MP solubilizes in alkaline solutions only. Dissolving precisely weighed 50 grams of 6MP in a volumetric flask with 0.1N NaOH produced a stock solution of 6MP. The flask was set on a sonicator to hasten the dissolving of 6MP, and at last the volume was brought up to the required level using the same solvent to provide a solution with a concentration of 1mg/ml. Five milliliters of this solution were pipetted out and diluted to the mark in a 500ml volumetric flask using a 1ml pipette, therefore producing a final strength of 0.01 mg/ml or 10µg/ml. This stock solution's lambda max was noted at 310nm. Further diluting this stock solution, seven dilutions of 6MP in the range of 8-0.1 µg/ml (8µg/ml, 6µg/ml, 4µg/ml, 2µg/ml, 1µg/ml, 0.5µg/ml, and 0.1µg/ml) were then stored in a stoppered flask and examined using UV Visible spectrophotometer for their absorbance (García & Jaramillo, 2023; Stoev *et al*., 2023; Yurievna *et al*., 2023). All the produced solutions' absorbance was noted at 310 nm, and a standard curve was created (Costa *et al*., 2022; Dipalma *et al*., 2022; Sugimori *et al*., 2022; Zhao *et al*., 2022). This standard absorption curve then helped one to determine the medication concentration in the serum of the rabbit. Data relevant to the absorbance for each concentration is shown in **Table 1**.

Table 1. Absorbance of Standard Solutions

Concentration (µg/ml)	Absorbance At 310nm
10	1.273
8	1.001
6	0.783
4	0.55
2	0.271
1	0.147
0.5	0.08
0.1	0.05

Experimental Design

Rabbits were selected at least two weeks ahead of the experiment so that they could be acclimatized to the experimental housing. Housing temperature was maintained at 30 ± 5°C, with twice the water, feed of crude protein, carbohydrates, and fiber were given to all selected subjects. To carry out the experiment, a fixed dose of 10mg/kg (Borel & Schwartz, 1964; Liver, 1999) of experimental medication Observing the absorption pattern and health of rabbits in a pilot research where they had 6MP orally in the doses of 5mg/kg, 10mg/kg, 20mg/kg & 50mg/kg led to the selection of 6MP. The absorption pattern was seen using a UV spectrophotometer following blood sampling, serum collection, deproteinization, and dilution (Iriti *et al*., 2024; Safa & Farkas, 2024).

Determination of Animal Group

One of the three groups, identified as A, B, and C, acted as the control group, while the other two groups, each consisting of six rabbits, were classified as treatment groups. A total of eighteen healthy rabbits were assigned to these three groups. Blood samples were taken from each rabbit in each of the three groups before any drug was administered. These blood samples were then utilized as a blank in the spectrophotometer once the drug was administered (Bei *et al*., 2023; ElKenawy *et al*., 2023; Kęska & Suchy, 2024; Kowalski *et al*., 2024).

Group A: Six distinct doses of 6MP by itself were created at a strength of 10 mg/kg using the weight of each rabbit and encapsulated in gelatin. The six rabbits comprising group A, which acted as the control experiment, were given these doses. The timing was noted precisely, and the pills allocated to each rabbit were meticulously given orally at this exact time.

Group B: Group B rabbits were given a usual dose of allopurinol of 20 milligrams per kilogram of body weight and 10 milligrams per kilogram of body weight of 6MP (Wisner & Renner, 1988; Wakuda *et al*., 2014). Weighing each rabbit helped us to identify the suitable quantities of allopurinol and 6MP to give to every single rabbit. At first, every one of the six rabbits got their allopurinol tablet according to their personal criteria. After thirty minutes, each rabbit received six milligrams of their allocated dose, and the time was noted.

Group C: As with previous groups, the weight of each rabbit in this group was measured, and the doses were calculated accordingly. All the 6 rabbits placed in group C were given their respective capsule of febuxostat 30 mins prior to giving their respective dose of oral 6MP.Group C rabbits received febuxostat (30mg/kg) (Khosravan *et al*., 2006; Chen *et al*., 2014) and 6MP (10mg/kg).

Blood Sampling

A blood sample of every rabbit was taken at set intervals of 40, 80, 20,160 & 200 mins once all three groups had received their individual capsules. Putting the rabbit in a restricting box helped to accomplish this. Shaving off the ear revealed the marginal vein. Rubbing the ear vein and putting the rabbit under a heat source, like a light, helped ethanol serve as an antiseptic and vasodilator. A pricking needle was used to prick the dilated vein, and a 2ml centrifuge tube collected the blood pouring out; it was then marked. To avoid hemolysis, blood was induced to run down the tube wall. Polymyxin B ointment was used later in the pierced area. To promote coagulation, the gathered blood was first held at room temperature for around five minutes and then in ice-cold water for about fifteen minutes. Every rabbit in all three groups underwent similar procedures.

Serum Separation and Analysis

Blood samples taken were centrifuged for 12 to 15 minutes at 5000rpm, isolating serum from blood cells. Vortexing a mixture made from moving 0.5ml (1part) of clear serum from each tube in a clear tube and adding 0.5ml(1 part) of acetonitrile into it deproteinized samples. Centrifugation at 4000rpm for 10 minutes on the deproteinized sera was done once again; the supernatant was then meticulously moved to a centrifuge tube. UV spectrophotometer analysis was conducted by diluting these samples with 0.1N NaOH, and reading (in µg/ml) were recorded at 310nm.

Data Analysis and Ethical Approval

Data collected for each group were then presented using descriptive statistics, i.e., frequencies, mean, and standard deviation, using SPSS version 21. One-way ANOVA was used to estimate the difference between the groups; a p-value less than 0.05 was considered statistically significant. The study protocol was approved by the research ethics committee of the University.

Results and Discussion

Results indicate that the concentration diminishes over time for all three groups (6MP, ALP, and FBX). This indicates that the chemicals are being digested or excreted from the body. Nonetheless, Group A exhibited a swift fall in concentration during the final assessment relative to Groups B and C. The results illustrate a distinct dose-dependent and time-dependent correlation in the concentrations of 6MP, ALP, and FBX in the animals' blood. Increased dosages result in elevated starting concentrations and reduced elimination rates. The concentrations of all chemicals diminish with time, signifying their processing and elimination from the body of the experimental animal. Further details are described in **Tables 2 and 3**.

Table 2. Concentration of regimen administered to all three groups at different time intervals

	Animal Code	Body Wt. (kg)	Dose admin in (mg)			Conc. in µg/ml at interval of (mins)				
			6MP	ALP	FBX	40	80	120	160	200
Group A	A1	1.39	13.97	-	-	2.34	4.31	1.12	0.46	0.03
	A2	1.43	14.27	-	-	1.81	4.44	1.38	0.76	0.23
	A3	1.59	15.99	-	-	1.19	3.29	1.19	0.53	0.07
	A4	1.50	14.98	-	-	0.46	2.63	1.98	0.79	0.03
	A5	1.58	15.89	-	-	1.56	3.63	1.77	0.70	0.06
	A6	1.31	13.16	-	-	1.46	3.12	1.55	0.71	0.08
Group B	B1	1.49	29.85	14.88	-	2.04	5.79	3.92	3.46	2.80
	B2	1.64	32.89	16.50	-	3.65	4.21	2.63	2.21	1.61
	B3	1.58	31.57	15.79	-	2.30	4.91	3.49	2.96	2.37
	B4	1.39	27.93	13.56	-	2.57	3.62	2.44	1.71	0.99
	B5	1.34	26.82	13.46	-	2.14	3.87	3.44	2.94	1.79
	B6	1.42	28.34	14.17	-	2.47	4.08	3.39	3.04	2.14
Group C	C1	1.64	49.18	-	16.39	10.35	15.65	14.49	11.50	10.47
	C2	1.49	44.83	-	14.98	8.26	11.22	9.04	6.48	4.39
	C3	1.36	40.88	-	13.66	6.23	10.67	10.40	10.20	7.37
	C4	1.43	42.81	-	14.27	10.20	12.97	9.94	8.13	6.67
	C5	1.41	42.40	-	14.17	9.06	11.90	10.68	9.24	6.82
	C6	1.47	44.02	-	14.67	9.27	12.05	11.10	9.08	5.85

Table 3. Comparison of Means across three groups

Time in minutes	Group A Mean ± SD	Group B Mean ± SD	Group C Mean± SD	F- (A)	p-value (A)	F-(B)	p-value (B)	F- (C)	p-value (C)
40	1.47 ± 0.63	2.53 ±0.58	8.9±1.52						
80	3.57 ± 0.70	4.42 ±0.80	12.41±1.77						
120	1.5 ± 0.33	3.22 ±0.56	10.94±1.88	5.99	0.006*	4.44	0.020*	14.07	<0.001*
160	0.66 ± 0.13	2.72 ±0.64	9.1±1.72						
200	0.08 ± 0.07	1.95 ±0.63	6.92±2.01						

One-way ANOVA was applied, p-value less than 0.05 was considered statistically significant.

The primary therapies for hyperuricemia and gout are allopurinol and febuxostat. By blocking purine base catabolism, these drugs lower uric acid production. Rarely are uricosuric drugs used to clear uric acid from the kidneys (Beara-Lasic *et al*., 2010). Unlike allopurinol, the novel XO inhibitor febuxostat, Structural variation results from allopurinol's purine ring, absent in febuxostat. Compared to allopurinol, febuxostat is 10-30 times more potent, selective, and free of adverse effects (Edwards, 2009).

Apart from their usefulness in impeding the production of uric acid, these XOIs are also studied for their effect on the oral bioavailability of 6MP, a drug that undergoes extensive first-pass metabolism involving the activity of XO. This pharmacokinetic parameter was evaluated using animals (rabbits) divided into 3 groups: A, B, and C, each containing 6 rabbits. The dose of 6MP used in the experiment was 10mg/kg. Six rabbits in group A received 6-mercaptopurine (6-MP) at a fixed dosage of 10 mg/kg. Blood samples were collected at different time intervals to determine the serum concentration of 6-MP. The mean concentration observed at the initial interval of 40 minutes was 1.45 µg/ml. The samples collected at 80 minutes and 200 minutes demonstrated peak plasma concentrations of 3.5 µg/ml and 0.082 µg/ml, respectively. The abrupt decrease in serum concentration of 6MP at the final interval can be attributed to the metabolism of 6-MP into inactive 6TU by liver or intestinal XO.

The group identified as B received a 20 mg/kg dose of allopurinol 30 minutes before the administration of 6-MP. Samples were collected at regular intervals. The values were distinct from those recorded for members of group A. The sampling results indicated a mean concentration of 2.5 µg/ml, a peak plasma concentration of 4.36 µg/ml, and a final interval concentration of 1.93 µg/ml at 40, 80, and 200 minutes, respectively. The observed difference in concentration of group B compared to group A can be attributed to the concomitant administration of allopurinol, which inhibited the activity of xanthine oxidase (XO) responsible for metabolizing 6-mercaptopurine (6-MP) in the previously studied group.

The rabbits in group C received febuxostat, an alternative xanthine oxidase inhibitor. 6-MP was administered to this group 30 minutes following the administration of febuxostat. The samples were subsequently analyzed. At 40 minutes, the concentration was 8.79 µg/ml, while the peak level at 80 minutes reached 12.26 µg/ml. At the final interval of 200 minutes, group C animals exhibited a concentration of 6.84 µg/ml of 6-MP. Group C, which received pretreatment with febuxostat, exhibited the highest concentrations of 6-MP among all groups. This study showed that the bioavailability of 6-MP increased at each interval when either allopurinol or febuxostat was administered before 6-MP, due to the inhibition of XO by these agents. Findings indicate that the concurrent administration of allopurinol and 6-MP resulted in an approximate doubling of the 6-MP concentration compared to its baseline level. The combination of febuxostat with 6-MP resulted in a concentration of 6-MP that was nearly six times higher than when 6-MP was administered alone. The increase is attributable to the interaction between XO inhibitors and 6-MP.

Change in bioavailability was observed with the use of allopurinol and febuxostat; however, there was no alteration in the time required to achieve peak plasma concentration. The results at the final sampling interval demonstrated the superior and prolonged XO inhibitory effect of febuxostat. Febuxostat exerts its mechanism of action through the non-competitive inhibition of the molybdenum pterin center, which serves as the active site on xanthine oxidase (Grewal *et al*., 2014). The intervention effectively reduces elevated uric acid levels due to its rapid onset of action, allowing for retesting of uric acid levels within two weeks of therapy initiation (Sundy *et al*., 2011).

Allopurinol and oxypurinol exhibit structural similarities with various purine compounds present in the body, which may lead to interference in purine and pyrimidine metabolism through the inhibition of other biological catalysts. No such interferences were observed with febuxostat. As a result, the enzymes, including orotate phosphoribosyltransferase, hypoxanthine-guanine phosphoribosyltransferase, guanine deaminase, orotidine-5′-monophosphate decarboxylase, and purine nucleoside phosphorylase, are not impacted (Chinchilla *et al*., 2016).

Increasing the dose of 6MP to reach the therapeutic concentration elevates the levels of pharmacologically active 6TGN, while concurrently raising 6MMP levels, which are implicated in hepatotoxicity (Broekman *et al*., 2017). To enhance efficiency and safety, 6MP is administered in conjunction with allopurinol and febuxostat. The XOIs inhibit XO activity, thereby impairing the production of inactive 6TU. The metabolism is consequently altered to enhance the production of pharmacologically active 6TGN metabolites (Gardiner *et al*., 2011).

It is evident from the literature that Allopurinol can increase the bioavailability of 6MP up to fivefold (Stockert & Stechschulte, 2010). Allopurinol metabolizes 6MP to synthesize 6TGN, which

is therapeutically more active and potent, and leads to undesired effects of 6MP. However, in addition to this enhancement in the bioavailability, which is somehow beneficial for the effect of 6MP, these higher levels can lead to the onset of undesired events like leukopenia and myelotoxicity (Schmiegelow *et al*., 2014). Therefore, it is recommended that this combination, i.e., 6MP-Allopurinol, must be avoided; if it's necessary, then it's important to adjust the dose of 6MP to one-third to avoid the chances of any potential undesired effects (Stockert & Stechschulte, 2010).

In addition to the increase in bioavailability, allopurinol has some beneficial effects. Co-administration of 6MP with allopurinol can lead to the decreased formation of 6MMP, thus reducing the hepatotoxicity of 6MP (Seinen *et al*., 2016). This approach of using allopurinol in combination is of great benefit to the patients suffering from inflammatory bowel disease (IBD) (Amin *et al*., 2014), autoimmune hepatitis (Deswal & Srivastava, 2017), and other associated disorders, who exhibit non-responsiveness or experience adverse effects from 6MP. Some studies have revealed that concurrent therapy with allopurinol results in a twofold increase in 6 TGN levels. A reduction of the 6 MP dose to 25-50% of the standard amount is recommended to mitigate myelotoxicity (Chouchana *et al*., 2013). Therefore, in addition to the impact of XO on the bioavailability of the 6MP, the safety of the 6MP and its dose must be adjusted based on the patient's needs so that the element of patient safety can be enhanced in the group of patients on therapy of 6MP (Blaker *et al*., 2013; Goel *et al*., 2015).

Conclusion

In conclusion, XO, including allopurinol and febuxostat, has a significant impact on the bioavailability of 6-mercaptopurine (6MP). Therefore, concurrent therapy of these two therapeutic agents requires careful consideration for enhancing therapeutic efficacy and ensuring safety by preventing the incidence of adverse events. Clinical data demonstrate a substantial enhancement in 6MP bioavailability after allopurinol pretreatment, necessitating careful dosage adjustments. Thus, the concurrent use of 6MP with XOIs requires a significant dosage decrease, often to one-third of the usual amount, to mitigate the potential of severe side effects. This underscores the critical necessity for meticulous monitoring and individualized dosing strategies to ensure patient safety and therapeutic effectiveness.

Limitations

One of the main limitations of this study is the lack of histological and longitudinal data to prove the impact of the interaction of 6MP and XO on efficacy and safety among the patients. Future studies should consider this specific aspect to rule out safety in an effective manner.

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Novelty of Research

This research has explored an interaction between 6MP and XO, which is of great clinical importance among patients suffering from inflammatory and oncological conditions. Future studies shall focus on developing dosing protocols that can assist in reducing the toxicity and enhancing the safety of this combination therapy among patients (Ambardekar *et al*., 2022; White *et al*., 2022; Al-Thani *et al*., 2023; Boujguenna *et al*., 2023).

Conflict of interest: None

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