TEACHERS' TOPICS

A Pharmacy Practice Laboratory Exercise to Apply Biochemistry Concepts

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Objectives. To develop exercises that allow pharmacy students to apply foundational knowledge discussed in a first-professional year (P1) biochemistry course to specific disease states and patient scenarios.

Design. A pharmacy practice laboratory exercise was developed to accompany a lecture sequence pertaining to purine biosynthesis and degradation. The assignment required students to fill a prescription, provide patient counseling tips, and answer questions pertaining to the disease state, the underlying biochemical problem, and the prescribed medication.

Assessment. Students were graded on the accuracy with which they filled the prescription, provided patient counseling, and answered the questions provided. Overall, students displayed mastery in all of these areas. Additionally, students completed a course survey on which they rated this exercise favorably, noting that it helped them to integrate basic science concepts and pharmacy practice.

Conclusion. A laboratory exercise provided an opportunity for P1 students to apply foundational pharmacy knowledge to a patient case and can serve as a template for the design of additional exercises.

Keywords: biochemistry, purine metabolism, gout, pharmacy practice laboratory, basic science, therapeutics

INTRODUCTION

The revised Accreditation Standards and Guidelines for the Professional Program in Pharmacy Leading to the doctor of pharmacy (PharmD) degree place an increased emphasis on a science foundation that provides a greater understanding of medication use in the treatment and prevention of disease.¹ Guidelines 10.2 and 13.1 specifically address this point and present both an opportunity and challenge for basic science faculty members to provide examples and applications of their respective topics to therapeutic decisions and clinical practice scenarios. While the greatest challenge lies in the ability to find adequate time and a suitable balance between the discussion of core principles and therapeutic applications, the use of case studies, assignments, and other venues for therapeutic applications provide an excellent opportunity for students to realize the importance of their basic science courses.

Alsharif et al evaluated and discussed a model to teach clinically relevant medicinal chemistry and provided an extensive reference of other ways to apply medicinal chemistry to clinical decisions.^{2,3} Roche de-

scribed a receptor-based approach that links the chemistry and structure-activity relationships of nonsteroidal anti-inflammatory drugs (NSAIDs) to therapeutic decisions.⁴ Similar efforts have been described in the *Journal* in the areas of physiology,⁵ biochemistry,⁶⁻⁸ pharmacology,⁹ and pharmaceuticals.¹⁰ Most of these articles not only emphasize the application of basic science to clinical practice but also describe activities that focus on enhancing critical thinking and problem-solving skills through case studies, computer technology, and smaller student work groups. These latter activities are excellent examples to help faculty address Accreditation Council for Pharmacy Education (ACPE) standard 11.2, a guideline that encourages faculty to apply a variety of teaching styles and learning methods to their respective courses.

This paper discusses initial efforts within the Mylan School of Pharmacy at Duquesne University to use a pharmacy practice laboratory exercise to address similar issues within a biochemistry course. Biochemistry is offered as a 2-course sequence in the first professional (P1) year of the school's 2-4 program. The fall course, Biochemistry I, is designed as a 4-credit lecture sequence that begins with introductory conceptual topics; progresses to discussions about amino acids, proteins, and enzymes; and is followed by discussions about carbohydrate and lipid metabolism. The last 3 weeks of the course

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involve discussions of the integration of carbohydrate, lipid, and protein metabolism and some specific disease states that arise from alterations of normal pathways. Additionally, students attend 5 laboratory sessions during the semester to apply knowledge gained in the areas of amino acids, proteins, and enzymes to particular laboratory scenarios. The spring offering, Biochemistry II, is a 2-credit course that focuses on nucleotides, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), the genetic code, protein synthesis, and gene expression and regulation. Similar to the fall semester, the spring course includes 2 traditional laboratory sessions and lecture applications to particular drugs and disease states. Additionally, a case-based exercise was developed based upon classroom discussions of purine biosynthesis, metabolism, uric acid, and gout. This exercise required students to apply topics that were discussed in lecture to a patient-based scenario held in the school's Academic Research Center for Pharmacy Practice.

The community pharmacy practice area of the center is a 900-square foot laboratory that houses state-of-the-art automation and dispensing technology, including the Pharmacy 2000 dispensing system, PharmaServ for Windows, Baker Cells, Baker Cassettes, and Baker APS Universal. The pharmacy also stocks nonprescription, prescription, and herbal medications, as well as home health care products such as wheelchairs, canes, walkers, diabetic and blood pressure monitors, and home testing kits.

The center has an audiovisual system that allows videotaping during mock counseling sessions. The room is equipped with directional microphones to record interactions that occur between students and mock patients. Students are able to view their recordings with the instructor, mentor, or facilitator and discuss their performance. A separate conference room, with a TV and VCR allows for this evaluation.

The main focus of the center is the pharmacy practice exercises. The motivation for the development of the exercises was to integrate, reinforce, and enhance the process of learning. All too often, students are left with a feeling of "why do I have to learn this material?" or "I'm never going to use this in real-life" (sentiments that often are reinforced by practicing pharmacists serving as preceptors). Students do not have the experience or the maturity at this point in their pharmacy career to understand the importance of the material that they are required to learn. Often they marginalize this material before they understand its applicability. The goal of this integration was to demonstrate to students the applicability of the information taught in lectures to the practice of pharmacy. In addition, it was designed to prepare them for their internship experiences. Each pharmacy practice exercise

requires the student to fill a prescription for one of the drugs used in the practice scenario.

All courses within the professional pharmacy curriculum were invited to participate in the center for pharmacy practice exercises. Similar exercises were developed for physiology, clinical microbiology, pharmaceuticals, clinical and drug information skills, pharmaceutical analysis, as well as for all of the school's integrated biomedical science and therapeutics courses. However, this article only focuses on an exercise developed to supplement biochemistry lectures and content.

DESIGN

The first topics discussed in Biochemistry II were a general overview of DNA structure and function, and the biosynthesis and degradation of nucleotides.¹¹ There were 3 general learning objectives for this section. After completion of this section, students should have been able to: (1) provide a detailed overview of the structure and function of DNA; (2) explain the overriding concepts in DNA synthesis and degradation, as well as regulatory controls governing these pathways; and (3) extrapolate information from the first 2 objectives to explain how alterations in DNA structure, synthesis, and degradation can lead to specific disease states. As part of this third objective, discussions of a number of relevant drugs were included.

While both purines and pyrimidines are essential for the biosynthesis of DNA, purine biosynthesis requires more enzymatic steps. This allowed for the discussion of many conceptual issues that could be applied to other pathways. This focus helped to address the second learning objective for this unit by emphasizing that the ability to learn and apply reaction concepts was much more important than rote memorization of specific pathways. As an example, a stronger emphasis was placed on the reason and mechanism for specific types of reactions (eg, dehydrogenase reactions) as opposed to requiring students to memorize all aspects of a reaction scheme. The logic behind this approach was that by focusing upon conceptual issues, students would be better prepared to apply these concepts to reaction schemes not covered in lectures.

Lecture Material Prior to Pharmacy Practice Lab Exercise

Purine biosynthesis occurs in 4 different stages, the first of which is the synthesis of 5-phosphoribosyl-1-amine (Figure 1). Key concepts introduced during this stage were the use of glutamine as a key source of nitrogen, the necessity to form 5-phosphoribosyl 1-pyrophosphate (PRPP) as an intermediate, and the role of pyrophosphate in driving reactions in the forward direction. Additionally,

Figure 1. The end products of the first 3 stages of purine biosynthesis.

the concept of “committed steps” was reviewed when discussing the conversion of PRPP to 5-phosphoribosyl-1-amine. The specific reactions for this stage, as well as stages 2 and 3 can be found in the Leninger text.¹¹

In the second stage, 5 atoms are added, glutamine is once again used as a nitrogen source, and 5-aminoimidazole ribonucleotide (Figure 1) is built upon the phosphoribosyl backbone. A key concept that was reinforced in this stage is the need to activate functional groups prior to the transfer of additional atoms. This concept was first discussed in the conversion of ribose 5-phosphate to PRPP, and is essential for subsequent reactions not only in the purine pathway, but also in pyrimidine biosynthesis and in other pathways. Three additional concepts introduced in this stage were the requirement of folate cofactors, specifically N¹⁰-formyltetrahydrofolate (N¹⁰-CHO THF), as a carbon source; the mechanism by which a linear chain can cyclize; and the mechanism by which oxygen can be displaced by nitrogen. This latter concept involves functional group activation prior to displacement.

The third stage requires 5 steps, results in the formation of inosine monophosphate (IMP, Figure 1), and provided additional examples of the use of amino acids as nitrogen sources, functional group activation, folate cofactor use, and ring closure. From a conceptual point of view, and with the exception of CO₂ acting as a carbon source, all of the steps used previously discussed reaction concepts. As previously mentioned, students were encouraged to learn reaction concepts and then apply them to similar pathways. This third stage provided an early opportunity to reinforce this idea.

The final stage (Figure 2) involves the conversion of IMP to either adenosine monophosphate (AMP, adenyate) or guanosine monophosphate (GMP, guanylate). Since each of the 4 reactions involved mechanisms previously discussed, this stage served as a final opportunity to reinforce mechanistic concepts. Students were not expected to memorize the names of all of the intermediates in this pathway, nor expected to memorize all of the enzymes; however, a strong emphasis was placed on students discerning the types of reactions that were occurring

and applying that knowledge. As an example, the conversion of IMP to xanthine monophosphate (XMP) involves the conversion of NAD⁺ to NADH and the addition of oxygen. Based upon concepts learned in the glycolysis pathway in the fall biochemistry course, students were expected to recognize that this was a dehydrogenase reaction. Since the substrate is IMP, students also were expected to correctly discern that the enzyme catalyzing the reaction was IMP dehydrogenase.

Following a presentation of the control mechanisms that govern purine biosynthesis, the course discussion shifted to purine degradation, uric acid formation, and gout. As shown in Figure 3, purine degradation proceeds via an initial removal of the phosphate and sugar to form either hypoxanthine or guanine. At this point, the purine bases can either be recycled back to AMP or GMP, respectively, or further degraded to uric acid. Two key points in the recycling pathway are that PRPP, 1 of the initial intermediates in purine biosynthesis, is once again used to provide the sugar-phosphate component of the nucleotide, and that this reaction, similar to the formation of 5-phosphoribosyl-1-amine, is a transferase enzyme. Once again, the similarities in substrates and mechanisms were emphasized so that students could better associate and learn the similarities in the original de novo biosynthetic pathway and in this salvage pathway. A key point in the hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) catalyzed recycling pathway is that 90% of the degradation products, hypoxanthine and guanine, are normally salvaged, and that only 10% are further metabolized to uric acid.

To help students link the basic science of purine metabolism and degradation to therapeutic situations, a brief discussion of hyperuricemia and gout was provided at this point in the lecture. Emphasis was placed on the following facts and concepts. The normal plasma solubility limit of uric acid is approximately 7 mg/dL; however, supersaturated solutions can readily form. Patients with uric acid levels greater than 7 mg/dL are diagnosed with hyperuricemia but do not immediately or necessarily develop gout. With a pK_a of 5.6, uric acid is approximately 98.5% ionized at a physiological pH of 7.4 and approximately 50% ionized at a urine pH of 5.6 (assuming a pH range of 5-6 for the urine). Since ionization increases aqueous solubility, uric acid is generally more soluble in the blood than in the urine. Normal blood pH is tightly regulated between 7.35 and 7.45, leading to an ionization range from 98.3% at a pH of 7.35 to 98.6% at a pH of 7.45. Thus, any minor increase in blood pH within normal limits will increase ionization and water solubility. The precipitation (or seeding) of urate crystals in joints and tissues can be caused by local pH changes, trauma, stress, cold, fluid depletion (ie, a local

Figure 2. Final stage of purine biosynthesis — the conversion of inosine monophosphate (IMP) to adenosine monophosphate (AMP) or guanosine monophosphate (GMP).

increase in uric acid) and/or a plasma urate-binding protein deficiency. Additionally, urate kidney stones may develop depending upon uric acid concentrations as well as any alterations of urine pH.

Students were asked to think about how genetic deficiencies could lead to gout. Specific answers were not discussed in lecture since this is part of the pharmacy practice laboratory exercise; however, students were encouraged to look at the pathways and control mechanisms that were discussed. A brief discussion of the approaches to treat gout was followed by a discussion of allopurinol and its mechanism of action. The newly approved xanthine oxidase inhibitor, febuxostat, will be included in future discussions. In general, the lecture material provided a basic framework, but not the specific answers to the questions they would encounter in the pharmacy practice laboratory exercise. The only exception was a detailed discussion of the mechanism of allopurinol (Figure 4). The exception was made to allow the instructor an opportunity to link the concepts of enzyme inhibition discussed in the fall Biochemistry I course to this particular compound.

Development and Application of the Pharmacy Practice Exercise

The director of the center, a practicing pharmacist, worked collaboratively with the faculty and course instructors to develop the pharmacy practice exercises. The initial steps involved a review of the course syllabus, the selection of an appropriate topic, and the development

of some key questions and a prescription for the drug or drugs pertinent to the exercise. Additional questions that integrated and “bridged the gap” between the lecture material and pharmacy practice were then written.

The staff members of the center, who were also actively practicing pharmacists, were involved in the development of the exercises. These pharmacists worked in a variety of practice sites and were able to offer different perspectives in the development of new exercises. It was deemed important to have actively practicing pharmacists involved in the development and implementation of the exercises. While the majority of faculty members were experts in their respective fields, the correlation of course material to pharmacy practice needs to be readily apparent to gain student acceptance. This was accomplished by utilizing pharmacists who were actively practicing in retail, hospital, long-term care, or another pharmacy practice setting.

Using this general procedure, a pharmacy practice exercise was developed to accompany the previously described lectures pertaining to purine biosynthesis and degradation. The exercise contained 7 questions (Appendix 1), as well as a prescription for allopurinol. Based on the case scenario presented in the exercise, students were expected to provide a plausible diagnosis (acute gouty arthritis, in this case), the underlying biochemical problem, a discussion of common symptoms and why they arise, potential genetic causes of this disease, the mechanism of action of allopurinol, a plausible solution for a potential drug interaction, and alternate therapeutic options. A grading key (Appendix 1) was developed to allow

Figure 3. Purine degradation, recycling, and the formation of uric acid. (Abbreviations: IMP = inosine monophosphate; AMP = adenosine monophosphate, GMP = guanosine monophosphate)

consistent grading across all students (average yearly enrollment in the course was approximately 150 students/class). Lecture material provided a beginning basis to answer these questions; however, students were expected to research available literature as well as information discussed in other courses, specifically physiology. Point values for the various questions were assigned based on question complexity and the amount of time required to research an appropriate response. While a few of the answers could be answered easily from course notes, most required consultation of additional resources and the application of course material to this specific patient case.

To complete this exercise, students were required to report to the Center for Pharmacy Practice during a 2-week time period, beginning after the topics had been discussed in class, and finishing prior to their next classroom examination. Reservations or "sign-ups" were not required. The center provided students with a number of timeslots including morning and afternoon slots every day of the week, 2 evening timeslots each week, and 1

weekend timeslot each weekend. Upon reporting to the center, students were given a copy of the prescription for allopurinol and were required to fill the prescription using computer software and the automated dispensing technology present in the center. As part of filling the prescription, students had to provide patient counseling information for the patient. Since all students in the school were required to have a PDA, this portion of the exercise provided an opportunity for students to research the pertinent counseling information using Epocrates, LexiComp, or other software packages. The students were not required to actually counsel a mock patient. Instead, they were required to submit a summary of the key counseling points they compiled regarding allopurinol. They then proceeded to answer a series of written questions relating to the completed prescription and to the material presented in the lecture, thereby connecting the information (Appendix 1). Since a major goal of this exercise was to help students have a clearer understanding of the application of their lecture material, instructors in the Center for Pharmacy

Figure 4. The mechanism of action of allopurinol.

Practice were available to direct the students to appropriate references and guide them through questions if needed. When finished, students submitted all of their work to a staff member for grading. Students were not required to make any oral presentations, nor were they asked to explain any of their answers to a staff member at the center.

EVALUATION AND ASSESSMENT

Student performance was graded according to the rubrics developed for the prescription and written ques-

tions (Appendix 1). The average student score for the first iteration of the exercise was 23.8/25 or 95%. Students also were asked to complete a short evaluation of this exercise. The survey instrument (Table 1) contained 8 Likert-scale items and 1 open-ended item to allow students to share their comments. Using a 6-point scale where 6 signified strong agreement and 1 signified strong disagreement, the overall response was very positive, with all questions receiving an average rating of 4.5-5.6. The 2 highest-rated statements indicated that students believed that this

Table 1. Student Responses to Exercise Evaluation Questions (N = 156)^a

Survey Item (Mean Response)	Strongly Agree, No.	Somewhat Agree, No.	Slightly Agree, No.	Slightly Disagree, No.	Somewhat Disagree, No.	Strongly Disagree, No.
Encouraged me to exercise my creativity (4.5)	11	75	52	16	1	1
Enabled me to experience situations that I would not have been able to otherwise (4.6)	31	63	36	18	6	1
Enabled me to visualize the ideas and concepts taught in this course (5.4)	95	36	22	1	1	0
Enabled me to apply key concepts (5.6)	104	39	12	0	0	0
Improved my ability to understand the general biochemical concepts (5.2)	55	78	17	4	1	0
Improved my ability to understand deeper implications of the course and exercises (5.1)	54	69	26	4	3	0
Improved my ability to link knowledge to previous learning (4.8)	38	69	36	9	3	0
Improved my ability to synthesize and integrate information from course offerings and exercises into practice (5.1)	56	64	30	5	0	0

^a Values listed indicate the number of students providing this response. Likert Scale: 6 = strongly agree to 1 = strongly disagree. Overall mean response is listed in parentheses.

exercise was beneficial to help them to visualize and apply key biochemical concepts. Student comments also were overwhelmingly positive. Of the 156 students who completed the survey instrument, all but 11 provided comments, with the vast majority providing positive feedback. Students stated that the exercise was extremely useful and/or interesting, and helped them to relate/apply lecture material to the practice of pharmacy, answer the “why do I need to know this?” question, prepare for the upcoming Biochemistry II examination, make a connection between biochemistry and pharmacy practice, and incorporate multiple concepts discussed in class to a realistic scenario. There were a few students who commented that they did not believe they had the knowledge or experience to answer a few of the questions posed in the exercise, and several others who stated that the exercise was too detailed and that “a patient would never ask these types of questions.”

DISCUSSION

The faculty members involved in developing the exercise were pleased with the level of student performance; however, the overall average did not show much discernment of student knowledge and ability. Some reasons for this include the ability to consult numerous resources, including one another, prior to submitting their answers. Even though students had to submit their own work, they were allowed to work together, thus making it a little easier to ensure that they had the correct response and the appropriate detail. Because this exercise is in the P1 year and 1 of several introductory integration exercises, the high average score was acceptable. While some adjustments can be made to attain a little more discernment, the general consensus among the faculty members involved was that the overall confidence gained by students applying foundational principles to patient scenarios far outweighed any minor effect on overall course grades.

Based upon the success of this collaboration, a number of additional exercises can be developed. These include variations of the case-based exercise described here as well as application of the exercise to other disease states. Enhancement of the described exercise can be accomplished by expanding the drug interaction questions and altering the primary scenario. While this initial exercise focused only on a drug interaction between allopurinol and 6-mercaptopurine, it can easily be expanded to include 6-thioguanine, a structural analog of 6-mercaptopurine whose metabolism is unaffected by allopurinol. This would provide a good example to illustrate how structurally similar compounds can undergo different metabolic pathways. Additionally, this assignment fo-

cused on primary gout caused by a genetic deficiency. With some adjustments, the focus of the case could be on secondary gout caused by a malignancy. One such scenario would be hyperuricemia caused by methotrexate remission induction therapy for lymphoid malignancies. A well-known drug interaction between allopurinol and methotrexate also could be incorporated into the case and questions. Applications to other disease states include the use of a cancer scenario to apply concepts taught in DNA replication, the use of an infectious disease scenario to apply concepts taught in protein synthesis, and the use of a diabetes scenario to apply concepts taught in glycolysis, fatty acid metabolism, and the overall integration of metabolism.

SUMMARY

The development of a pharmacy practice laboratory exercise to supplement lecture material in a P1 biochemistry class allowed students to apply the knowledge they gained to a specific disease and patient scenario. Specifically, the exercise allowed hands-on application of how alterations in DNA metabolism can lead to gout and provided an example of 1 potential treatment option for this condition. As such, this exercise helped to achieve a key learning objective for this unit (ie, the ability to extrapolate information and explain how alterations in DNA structure and pathways can lead to specific disease states). Overall, students performed well on this exercise and rated it favorably.

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Appendix 1. Questions for Pharmacy Practice Laboratory Exercise (15 points)

The answers (and minimal acceptable responses) are in italics, and are not present in the exercise sheet given to the students. While not shown here, students are given the structure of allopurinol as a reference. I.W. is a 45 year old male who enters your pharmacy with a prescription for allopurinol 200mg PO once daily. I.W. does not have a medical history of any other disorders. He informs you that he visited his physician because he had been experiencing severe pain in his big toe over the course of the past week.

1. What diagnosis was most likely made for I.W.? (1 point)
Acute gouty arthritis (or just gout)
2. What underlying biochemical problem caused the severe pain in his big toe? In answering this question, please make sure you include the following: the offending compound, the normal plasma levels of this compound, an estimation of the plasma level of this compound in I.W., and the biological source of this compound. (2 points)
*Uric acid concentration in the plasma has exceeded its solubility limit. In normal subjects, plasma becomes saturated with sodium urate at a concentration of 7 mg/100 ml; however, supersaturated solutions readily form. Patients with a blood concentration of uric acid which is > 7 mg/100 ml are **hyperuricemic**. Hyperuricemic patients are predisposed to gout. Seeding of urate crystals can be caused by: local pH changes, trauma, stress, cold, and/or a plasma urate-binding protein deficiency. Students should provide an estimate that exceeds 7mg/100 ml. The precipitation/deposition of uric acid leads to acute and chronic inflammatory responses. In terms of biological source, students should provide an explanation that uric acid (ionized form = sodium urate or just urate) is the end metabolic product of purine metabolism.*
3. For this particular condition, 50% of all patients experience initial attacks at the metatarsophalangeal (MTP) joint (ie, big toe), and over 90% of patients will, at some point, experience attacks at the MTP. Why does this condition tend to strike the MTP and other lower extremities (instep, knee, ankle) more than upper extremities (wrist, fingers, elbow)? (2 points)
There are two main reasons here. The first has to do with solubility. It should be noted that the precipitation of uric acid can be caused by cold. As the temperature decreases, the solubility of uric acid decreases. In general, the extremities receive less circulation and are colder than other parts of the body (think about it—how many times do your feet get cold as compared to your neck or back or upper leg?). This then targets the toes and the fingers, so why the toes. The reason is simple. There is more synovial effusion with weight-bearing joints.
4. While there are several potential causes for I.W.'s condition, identify one genetic deficiency that could cause this problem. Please include an explanation as to how this genetic deficiency contributes to the underlying biochemical problem you identified in question 2. (3 points)
*There are two correct answers here based upon the information presented in lecture. It is possible that students may put forth a plausible answer beyond these two. See your instructors if you have a question. The first reason is a deficiency in the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRTase). It is OK if students use the initials here. This enzyme **recycles** purines and is part of the normal "salvage" pathway for purines. If there is a genetic deficiency of this enzyme, there will be less recycling and salvaging and more degradation to uric acid. As a result, uric acid concentrations will increase. This also increases the available concentration of 5-phosphoribosyl 1-pyrophosphate (PRPP, initials OK), thus resulting in increased purine biosynthesis. The second reason is a mutation in PRPP synthetase enzyme. The enzyme has impaired allosteric regulation (ie, feedback control) causing an excess production of purines (increased purine synthesis). Since the concentration of purines will then exceed what is needed for biosynthesis of AMP and GMP, there will be enhanced breakdown and increased uric acid.*
5. What is the mechanism of action of allopurinol in treating I.W.'s condition? Be as complete and specific as possible. (2 points)
*Allopurinol is a prodrug. It is both a substrate and a weak inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid. In the body, allopurinol is oxidized to oxypurinol. In the process, oxypurinol remains tightly bound to xanthine oxidase and traps molybdenum in its reduced Mo^{+4} state. Since, the oxidized Mo^{+6} state is required for enzyme activity, xanthine oxidase is inhibited, and the production of uric acid is decreased. There is also an **increase** in the plasma levels of the substrates xanthine and hypoxanthine; however, these*

compounds are much more water soluble than uric acid. Allopurinol acts on purine catabolism, reducing the production of uric acid without disrupting the biosynthesis of vital purines.

6. 6-Mercaptopurine, an antitumor agent, is normally dosed at 200 mg PO once daily. Its metabolism is inhibited by allopurinol. **WITHOUT CONSULTING ANY REFERENCES**, which of the following courses of action would be the best? Provide justification for the answer you choose and for **ONE** of the answers you didn't choose. (3 points)
- Reduce the dose of allopurinol to 100 mg PO once daily.
 - Reduce the dose of 6-mercaptopurine to 100 mg once daily.
 - Change the dose of 6-mercaptopurine to 100 mg BID

Please Note: Points will be deducted for answers that appear to be copied from textbooks.

Answer a is an inappropriate choice. By decreasing the dose of allopurinol by 50%, there is a significant chance that the patient will experience increased acute episodes of his gout.

Answer b is the best choice (but actually a little higher than reference texts would recommend). I did this on purpose to assure that students were "thinking this through" and not just copying. The obvious reason for this response is that since 6-MP's metabolism is being inhibited, there will be increased concentrations of 6-MP accumulating unless the dose is decreased.

Answer c could be given partial credit; however, the patient is still receiving the same amount of 6-MP over a 24 hour period. There still will be accumulation and toxicity due to inhibition of metabolism.

7. If allopurinol does not successfully treat I.W.'s condition, what other compound could be recommended to decrease the offending compound you listed in question 2? Please provide a BRIEF mechanism for this compound. (2 points)
- Probenecid or sulfinpyrazone. These compounds increase the excretion of uric acid by blocking the active renal reabsorption of uric acid (I would also accept: blocks active renal transport of uric acid or organic acids). Please note that colchicine is incorrect here since it does not alter uric acid levels.*