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TEACHERS' TOPICS

Medicinal Chemistry and Therapeutic Relevance of Angiotensin-Converting Enzyme Inhibitors

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Chemical Basis of Drug Action (PHA337 and PHA447) is a required 2-semester course sequence taught to second-professional year pharmacy students at Creighton University in both the campus and distance-education pathways. The course emphasizes integration of previous content, critical thinking, and therapeutic relevance. The content and learning experiences are organized to transition the students' thinking through a constructive process that provides ample opportunities to recall and integrate previous knowledge, learn and apply new knowledge, establish a logical connection between the science and its therapeutic relevance, and finally to apply the science knowledge to predict clinical activity and clinical outcomes as can be expected in a patient. This manuscript is based on the angiotensin converting enzyme inhibitors as an illustration of how our course objectives are accomplished.

Keywords: medicinal chemistry, angiotensin converting enzyme inhibitors (ACEIs), therapeutics, critical thinking

INTRODUCTION

Drug chemistry is an essential component of understanding drug action. In our 2-course sequence of medicinal chemistry, the emphasis is on applying knowledge of drug chemistry to therapeutic decision making. To accomplish this, students are always challenged to recall previous content learned, critically analyze new drug chemistry knowledge in the context of previous information gained, and apply the overall knowledge to specific patient case scenarios. Many aspects of the strategies utilized in our course, including the structurally based therapeutic evaluation (SBTE) concept, case studies, problem-based learning, critical thinking exercises, simulations, and learning games, have been utilized, described, published, and tested over the years.[1-12] Over the last 2 academic years 2005-2006 and 2006-2007, the above strategies were all standardized in an approach for delivery of course content and course activities.[1] Our main goal from this standardized approach is to enhance student ability to apply this science, prior basic science information, and future therapeutic knowledge to make therapeutic decisions and to envision utilizing this knowledge in practice. In this manuscript, we will describe how our techniques are utilized in one lesson plan, angiotensin converting enzyme inhibitors (ACEIs), to meet the overall course objectives.

Lesson objectives are linked to Bloom's Taxonomy of Learning[1,13] and are as follows for the ACEIs:

- Discuss the rationale behind synthesis of ACEIs (Comprehension: II).
- Explain the therapeutic uses of ACEIs (I) based on their mechanism of action (Comprehension: II).
- Illustrate the rationale behind the history of the discovery of ACE structure and ACEIs. (Analysis: IV).
- Explain the structure activity relationships (SAR) of captopril, enalapril, and phosphorous containing analogs including SAR that impacts potency, oral activity, side effects and duration of action (Comprehension: II).
- Predict the oral activity and intravenous use with the different products (Application: III).
- Apply the knowledge of the SAR of this class of drugs (Application: III) to justify therapeutic decisions based on SBTE patient scenarios (Evaluation: VI).

DESIGN

Chemical Basis of Drug Action (PHA337 and PHA447) is a 2-semester required course sequence taught to second-professional year pharmacy students at Creighton University in both the campus and distance-education pathways. The campus-education pathway is

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taught on the traditional campus and the distance-education pathway is completed through predominantly distance education.[14] Campus and distance-education students are admitted to a 4-year doctor of pharmacy degree program after completing a minimum of 2 years of prepharmacy studies. The *Chemical Basis* courses meet in a classroom hardwired for laptop computer use on the desktop. Distance-education students are scattered throughout the country. However, they follow the same outline for the on-campus students, are required to meet the same learning objectives, and must complete the same evaluation strategies in the same timeframe. The students in both pathways use the same course web site, which is authored in Microsoft FrontPage 2003.

Students in the *Chemical Basis* courses have completed first-professional year curriculum, which includes semester-based coursework in biochemistry, physiology, pathology, anatomy, pharmaceutics, and communication skills. Students in the second-professional year curriculum concurrently enroll in a 10-credit-hour sequence in pharmacology (fall and spring) and a 4-hour course in microbiology (fall), along with the medicinal chemistry course sequence. Therapeutics is taught in their third-professional year.

The *Chemical Basis* lesson is a complete packet of information and learning aids organized in handouts, PowerPoint presentations, video, and screen-capture presentations, all linked to the course web site. It is designed to thoroughly integrate previous content, introduce and practice new content, and apply new content related to a drug class to clinical situations. Each *Chemical Basis* lesson consists of 6 discrete elements. The lesson elements include: (1) learning objectives, which are concise, performance-based statements that are designed to focus students' study and help them understand the level of content mastery expected of them; (2) a lesson handout, which is a standardized template for transitioning the student through the content, from recalling information to applying, illustrating, predicting, and analyzing it (lesson handouts are intentionally written to be descriptive, conversational, and reinforcing by asking key concept questions, so that they are clear, complete, interactive, and enjoyable to read); (3) a lesson summary of the most important "take home" messages; (4) a pre-class assessment quiz to help the students become familiar with the content before the official lesson session and to come prepared for an interactive class/online session; (5) interactive in-class PowerPoint slide presentation and discussion that guides and challenges the students to apply the knowledge in the classroom setting and in online discussions; (6) SBTE cases which expect the students to apply the knowledge to scenarios involving different patients with various co-morbidities.

Each lesson handout is divided into 6 sections: I. Introduction; II. Pharmacophore; III. SAR; IV. Applying the SAR; V. Summary of Common Clinical Decisions; and VI. Prediction of Clinical Activities. This template transitions the students' thinking through a constructive process that provides ample opportunities to recall and integrate previous knowledge (Section I), learn and apply new knowledge (Sections II and III), establish a logical connection between the science and its therapeutic relevance (Sections IV and V), and finally, apply the science knowledge to predict clinical activity and clinical outcomes in a patient (Section VI).[1-4,9,11] To describe this in more detail, the ACEIs lesson from the academic year 2006-2007 for both the campus (n = 109) and distance-pathway students (n = 50) is provided as presented to the students. The handout for this lesson and all lessons in the chemical basis of drug action course sequence is based on a thorough literature search of major medicinal chemistry textbooks,[15-17] therapeutics textbooks[18, 19] and primary literature.[20-24] Students are also referred regularly to review their notes and textbooks in anatomy, physiology, biochemistry, microbiology, and pharmacology.

Lecture Content: "ACEIs: A Fascinating Story in Rationale Drug Design"

Introduction. ACE catalyzes the conversion of angiotensin-I to angiotensin-II (Figure 1). Angiotensin-I is 10 amino-acid long while angiotensin-II is 8 amino-acid long (i.e.) ACE cleaves 2 amino acids from angiotensin-I to form angiotensin-II. Angiotensin-II is responsible for maintaining blood pressure homeostasis because it produces several hemodynamic effects including direct vasoconstriction by acting on angiotensin subtype-1 (AT_1) receptors, increasing aldosterone release, and increasing sympathetic nervous system effect, which ultimately result in an increase in blood pressure (the former 2 are the most important actions of angiotensin-II and are designated in bold in Figure 1). However, if present in abnormal amounts, this could predispose the individual to hypertension and heart failure.

Integration Exercise: *Recall and integrate essential knowledge in chemistry, anatomy, physiology, biochemistry, and other disciplines that are critical for understanding concepts related to ACEIs, their mechanism of action and their therapeutic use (Bloom's Taxonomy I & II: Knowledge and Comprehension, respectively).*

ACEIs act by lowering angiotensin-II in blood and tissue by inhibiting the conversion of angiotensin-I to angiotensin-II. This results in the reversal of the hemodynamic and neurohormonal abnormalities of hypertension

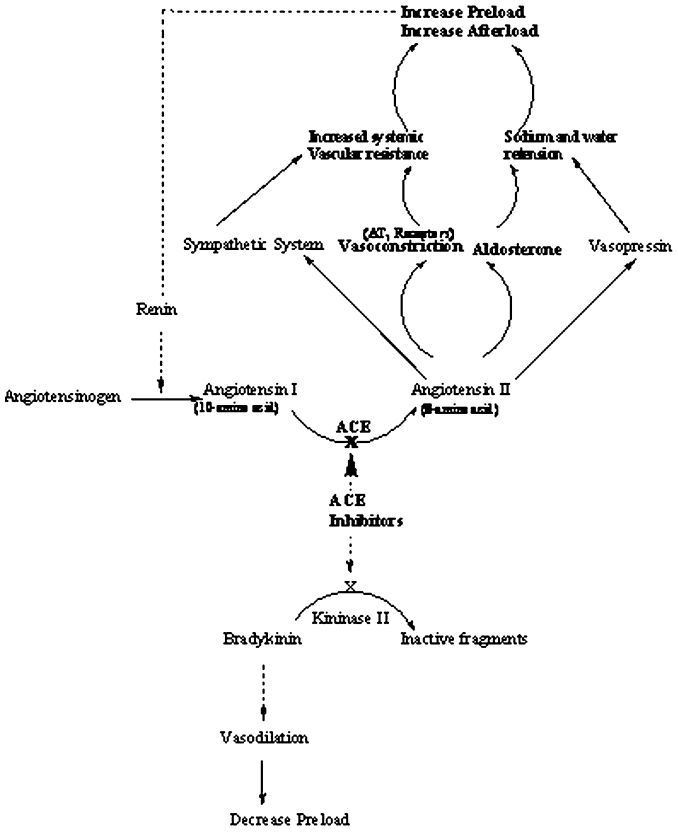

Figure 1. Schematic diagram of ACEIs actions (bold designates most important actions).

and heart failure. By preventing the formation of angiotensin-II, ACEIs also cause a decrease in the production of aldosterone resulting in hyperkalemia (Why would this be important?) (Table 1). As also shown in Figure 1, ACEIs inhibit degradation of bradykinin by kininase. This causes an elevation of bradykinin which is thought to be responsible for persistent dry cough and angioedema associated with ACEIs (Table 1). In addition, from Figure 1 (not the focus of this manuscript), we can see that once produced, angiotensin-II can bind to its receptor AT_1 to cause vasoconstriction which is one of its most important actions. Therefore, from a rational drug synthesis point of view, antagonists at the angiotensin-II receptor make sense since these compounds will most likely help to decrease blood pressure. Therefore, based on the physiological effects of ACE, it is reasonable to predict potential therapeutic usefulness for ACEIs in such disease states as hypertension and heart failure. The algorithm for management of key disease states such as hypertension are usually introduced at this point as summarized by Saseen and Carter[18] or by the Joint National Committee (JNC-VII)[20] to encourage students and challenge them to integrate prior, current, and future knowledge, and to emphasize the therapeutic relevance of the information presented.

Pharmacophore. Students are required to recognize the pharmacophore and it is required in our course. It is the same as remembering drug names in pharmacology, but in this case the emphasis is on recognizing potential drug action/class by the basic pharmacophore in the structure. To help relate to the essential/important functional features that impact activity, the critical functional features are identified by different colors. (Readers are encouraged to click on the ACEIs lesson linked in the Table of Contents on the PHA 337 website to see in more detail how course information is presented and communicated including the utilization of color and how course activities are organized and transitioned for each lesson plan (Go to http://pharmacyonline.creighton.edu/pha337; enter user name: spahpweb2\guestpha337; and password: 337Guest).

Previous studies with substrate and inhibitors of ACE suggested that this peptidase is a carboxypeptidase similar to pancreatic carboxypeptidase A (PCPA). PCPA has a zinc binding site and a cationic binding site. Therefore, ACE should have those 2 important active sites (Figure 2). Other auxiliary binding sites also exist. Based on the above and on concepts in rational drug design, 3 classes of ACEIs were developed including the captopril, enalapril, and phosphorous analogs. They all have functional features that allow them to bind to both the cationic and zinc binding sites of ACE. Figure 3 is a summary of the structures and names of the 3 pharmacophores. More detailed discussion related to the pharmacophores can be accessed from the course web site and from the sections below.

Structure Activity Relationship (SAR). *Captopril Analogs (sulfhydryl-containing inhibitors)*. In this rational drug design for the first ACEIs, we know so far that the inhibitor should have a group that enables it to bind to the cationic binding site and another group that enables it to bind to the zinc binding site. Other auxiliary binding sites

Table 1. Summary of Effect of ACEIs Actions on Angiotensin II, Aldosterone and Bradykinin.

Chemical/Hormone	Effect	Pharmacological Action
Angiotensin II	Decrease Angiotensin II	Decrease blood pressure.
Aldosterone	Inhibits aldosterone	Result in potassium retention (i.e.) hyperkalemia.
Bradykinin	Inhibits breakdown of bradykinin	May be responsible for the dry cough and angioedema.

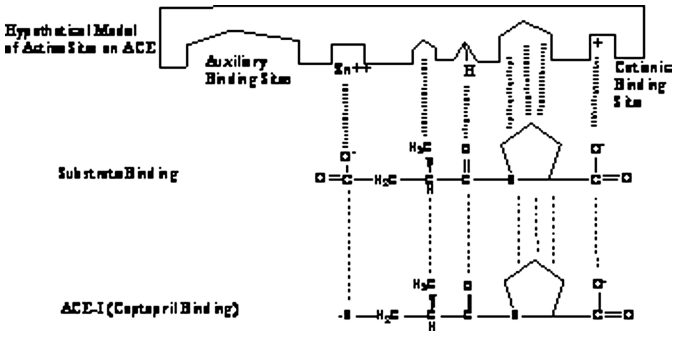

Figure 2. Schematic model of active sites of angiotensin converting enzyme.

may also exist, and when accommodated will enhance the potency of ACEIs by increasing the binding affinity to ACE. We also know that all naturally occurring peptidic inhibitors of ACE have proline as the carboxylic terminal residue. The carboxyl group on proline is essential for ion-ion bonding to the cationic site on ACE as shown in Figure 4, A.

Earlier, angiotensin-I was described as a 10 amino acid peptide and angiotensin-II as an 8 amino acid peptide (Figure 1). Therefore, ACE cleaves 2 amino acids from its substrate to produce angiotensin-II. As a result, ACE is termed a "dipeptidyl" carboxypeptidase (i.e.) it cleaves 2 amino acids. This means that the distance between the cationic binding site and the zinc atom binding site should be greater than in PCPA (which cleaves only 1 aromatic amino acid from the carboxylic terminal of a peptide in a protein meal) by approximately the length of 1 amino acid residue. Therefore, to extend on the proline to enable

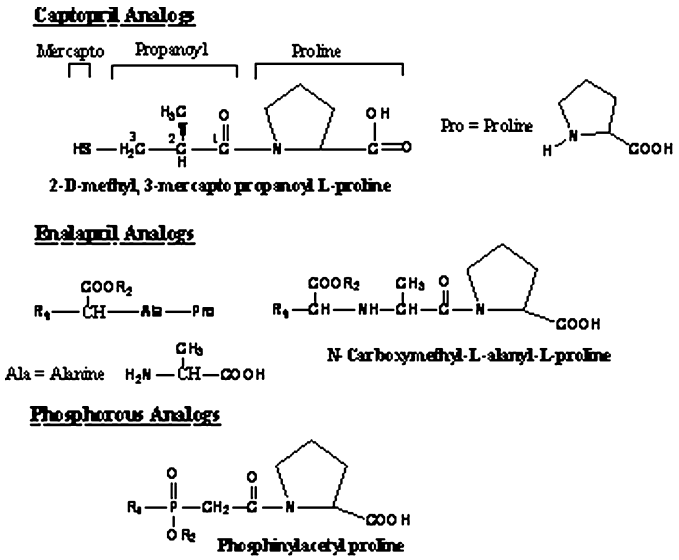

Figure 3. Angiotensin converting enzyme inhibitors pharmacophores.

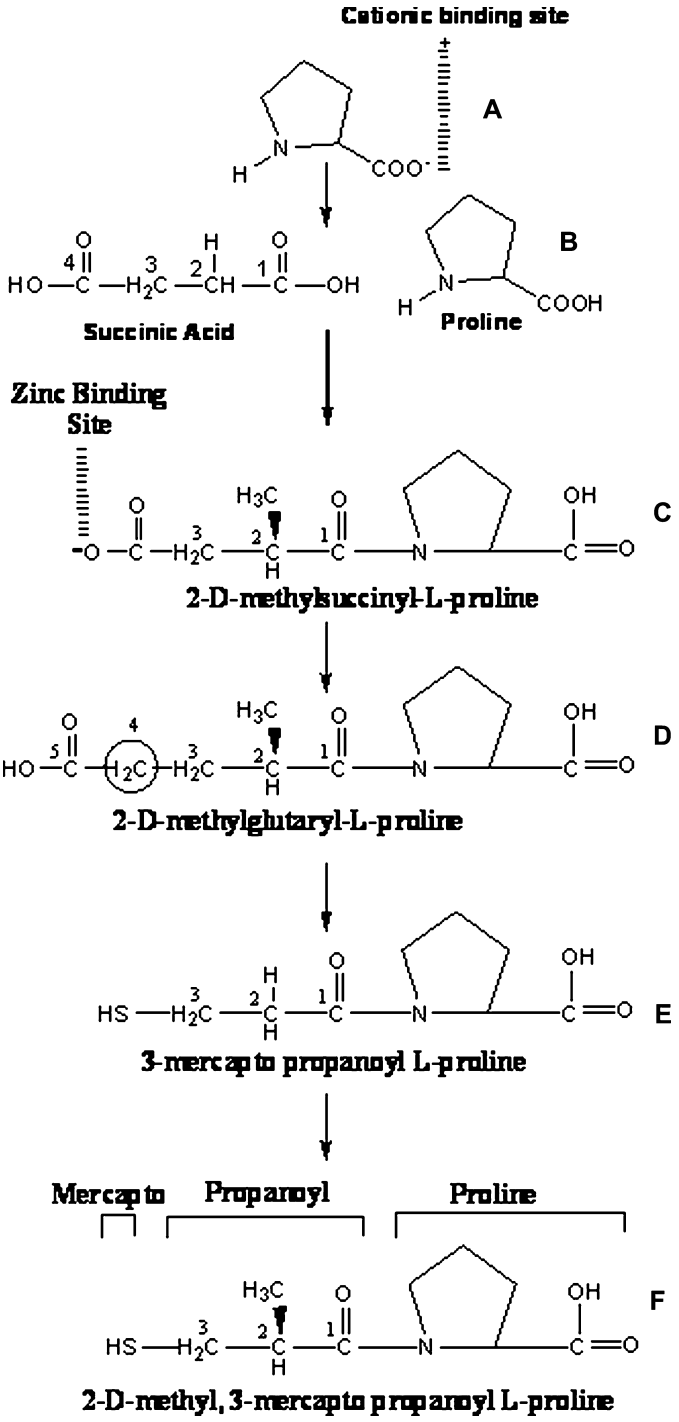

Figure 4. Illustration of the synthesis of captopril analogs.

it to bind to the zinc binding site, succinic acid was added to L-proline (the carboxylic group at $-C_1$ of succinic acid forms an amide bond with the amino terminal of proline). This resulted in a prototype compound that is slightly active but is a specific inhibitor of ACE (Figure 4, B). The effort was then shifted to structural modifications including substitution on the side chain and increasing the length of the side chain:

- The addition of a methyl group at the $-C_2$ of succinic acid (2-D-methylsuccinyl-L-proline) resulted in considerable increase in inhibitory activity of the prototype compound (Figure 4, C). Increasing the length of the side chain by adding another methyl to succinic acid (ie, glutamic acid) did not enhance the activity over the succinic acid derivative (2-D-methylglutaryl-L-proline, Figure 4, D).

So, what is the next rational step in the synthesis of an ACEIs? Well, if the student guessed modifications to the zinc binding carboxyl group on the succinic prototype, the answer would be correct. In fact, replacement by a mercapto group (-SH) led to a dramatic improvement in inhibitory potency without any concomitant loss of specificity (3-mercapto propanoyl-L-proline) (MPP) (Figure 4, E). The 2-D-methyl of (MPP) improved activity and produced the first marketed ACEI, captopril (Figure 4, F).

Enalapril Analogs (N-carboxymethyl-L-alanine-L-proline) & Phosphorous Containing (phosphinyl Proline) Analogs. Captopril (Figure 5) had a number of disadvantages including low potency, taste disturbances, allergic reactions, and short duration of action. The mercapto group contributes to all of the above problems.

So, what would be the next rational step in the synthesis of ACEIs? Well, if the student rationalized "to get rid of the mercapto group" he/she would be correct. Also, since we know that there are auxiliary binding site(s) next to the zinc binding site, then adding groups to accommodate the appropriate nature of this/these sites may enhance the potency of the resulting compounds. So, examination of the pharmacophore of the enalapril analogs in Figure 3, demonstrates similarity to what we saw in the captopril analogs with proline at the cationic site and now we see the second amino acid being alanine. Off the N-terminal of the alanine we have the methyl group which has a carboxylic group replacing the mercapto group. This is essential for binding to the zinc binding site. The R_1 substituent now extends the compound to bind to an auxiliary binding site. To enhance the potency over the captopril analogs, modifications were made to find the appropriate functional feature that can bind to the auxiliary binding site(s) next to the zinc binding site. Derivatives with different substituents for R_1 were synthesized with the derivative with a phenyl ethyl group for R_1 and with the S-configuration producing the best activity. Most marketed compounds have the phenyl ethyl group, indicating the presence of an auxiliary binding site next to the zinc binding site that can accommodate hydrophobic/Van der Waal bonding, resulting in compounds with higher affinity that are more potent than captopril analogs.

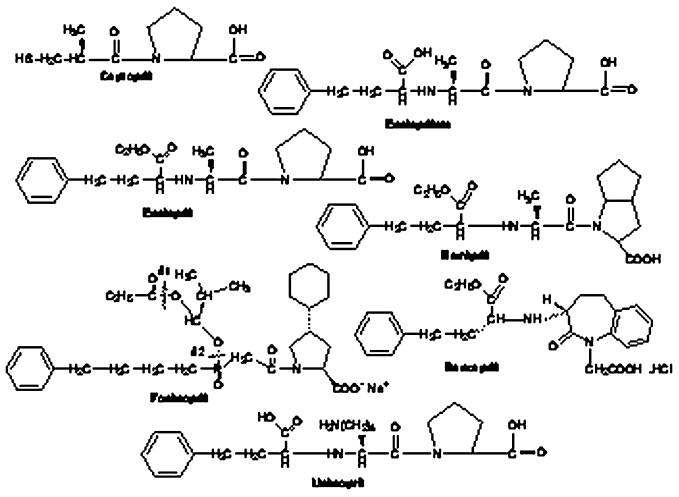

Figure 5. Marketed ACEIs.

- For the enalapril analogs, the R_2 substituent is either a -H (enalaprilate, Figure 5) or an ethyl (enalapril, Figure 5). The –H results in an active structure that is water soluble and is given by the intravenous route. The ethyl forms an ester with the carboxylic group and since the carboxylic group is now masked, it can not bind to the zinc binding site and the resulting compound is enalapril (Figure 5). The ethyl also adds lipophilicity and allows for better absorption and oral activity. The hydroxyl group of the phosphinyl group of the phosphorous analogs can also be made into an ester by substituting an alkyl group for the R_2.
- Cyclic amino acids such as proline confer particularly high activity at the dipeptide's carboxyl terminus. The cyclic nature provides for steric hindrance to amide bond hydrolysis and allows for therapeutic utility.
- The proline ring itself was tolerant of extensive variations (Figure 5). For example, adding a cyclopentane (eg, ramipril) or cyclohexane (eg, fosinopril) is acceptable. Also, incorporating the proline into a seven-membered ring structure is acceptable (eg, benzapril).
- The side chain -NH is important for inhibitory activity. Removal will dramatically decrease activity (400X).
- The carbonyl oxygen and the methyl group on the side chain may be involved with hydrogen bonding and hydrophobic bonding to the enzyme, enhancing affinity.
- Substituting an aminobutyl $H_2N(CH_2)_4$- for the side chain methyl makes the second amino acid lysine, thus, the name of the marketed product, lisinopril (Figure 5). The aminobutyl group

enhances oral bioavailability of lisinopril even without the presence of an ester at the side chain carboxylic group. It is dosed once a day.

- For the phosphorous containing analogs (eg, fosinopril, Figure 5), the main difference is that the zinc binding group has been modified to a phosphorous containing group (O = P-OH, phosphinyl). The alanine for the second amino acid is replaced with an acetic acid (CH_3COOH). However, the optimal distance is maintained to bind to both the cationic site with the carboxylic group of proline and with the anionic OH of the phosphinyl group to the zinc binding site. The size of the phosphorous atom is critical for maintaining the appropriate distance.

Applying SAR. In this section, there are examples of how to apply the knowledge of SAR to marketed products (for the purpose of this manuscript, one example is provided below). The same approach can be used to explain the activity of other marketed products and to become comfortable with applying the SAR knowledge. In addition, the learning experiences web page on the course web site has links to several application activities to help the students apply the SAR including: SBTE case scenarios and concept questions based on in the in-class presentation.

Example 1. Enalapril (Figure 5) is an N-carboxymethyl L-alanyl-L-proline derivative. It has the phenyl ethyl group at the side chain attached to the methyl carboxyl group, which enhances activity by allowing hydrophobic/Van der Waals bonding to the auxiliary binding site. The proline carboxylic group binds by ion-ion bonding to the cationic binding site. However, there is an ester on the side chain carboxylic group. Therefore, for the structure to bind to the zinc binding site, hydrolysis of the ester should occur first to provide for the free –OH group. So, enalapril is a prodrug. The ester also provides for increased oral absorption and bioavailability resulting in once-a-day dosing. The cyclic nature of the proline provides for an amide bond that is protected and not easily hydrolyzed by amidases. The carbonyl oxygen may be involved with hydrogen bonding. The methyl on the side chain may be involved with hydrophobic bonding, and the –NH is critical for activity by providing for hydrogen bonding to the enzyme. All of the above enhance affinity for the enzyme and make enalapril an orally active ACEI.

Summary of the Most Common Therapeutic Decisions. In this section, is a concise summary of some of the most common therapeutic decisions for this class of drugs (Table 2). The emphasis is on identifying clinical decisions that are explained by the drug structure. All of these decisions are emphasized in the in-class and online activities. Armed with the SAR knowledge and the clinical decisions, this will help apply the knowledge on all course evaluation activities. The following case provides a step-by-step approach of how to conduct an SBTE analysis based on an understanding of key SAR and therapeutic concepts related to ACEIs.

Cardiovascular SBTE Case Study Example. *NA, a 55-year-old white male is referred to the family practice clinic with complaints of nightmares, fatigue, and insomnia. NA has smoked cigarettes since he was a teenager, and has a 4-year history of hypertension that has been poorly controlled with compound 1 and compound 2 (Figure 6). Physical and laboratory assessment reveals a well-developed, overweight individual with the following clinical data: blood pressure, 160/100 mm Hg (110/85); potassium, 3.2 mEq/L (3.5-5.3); uric acid, 6 mg/dl (3.5-7); creatinine clearance (Clcr), 2 ml/min (90-120); total cholesterol, 280 mg/dl (< 200 mg/dl). NA has a history of noncompliance. Would switching from compound 1 (Figure 6) to enalapril (Figure 5) be a good therapeutic decision? Provide a SBTE for your answer.*

The student should recognize that enalapril is an N-carboxymethyl L-alanyl-L-proline (an enalapril analog, an ACEI). From the required anatomy and physiology readings, the student should be aware that the major site of production of the vasoconstricting peptide, angiotensin-II, is the blood vessels. The physiological responses to this substrate include an increase in systemic vascular resistance, increase in blood pressure (after load), and increase in pulmonary capillary wedge pressure (preload), all leading to decreases in cardiac output and perfusion of vital organs (heart, kidney). Since ACEIs prevent the formation of angiotensin-II, these adverse cardiovascular sequels will be prevented. Therefore, the biochemical and physiological characteristic of ACEIs make this class of drugs a viable choice for treatment of HT. From study of intermolecular interactions in organic chemistry and understanding of the structure of the ACE enzyme from biochemistry and physiology, the student should recognize that ACEIs have the structural features needed to bind electrostatically to the cationic and zinc-binding sites of the enzyme. The 2-amino-acid distance between the 2 ionizable sites is critical, and optimal in the marketed ACEIs, such as enalapril. It also has an ester which provides for good oral bioavailability and once a day dosing. Further, since the patient is white, and Caucasians have higher levels of renin, ACEIs are more effective. Finally, since compound 1 and 2 (Figure 6) are not controlling the patient's hypertension, switching the aryloxypropanolamine beta antagonist, compound 1, to an ACEI (enalapril, Figure 5) may help the patient, especially when the ACEI is combined with compound 2 (a

Table 2. ACEIs Common Therapeutic Decisions

Common Therapeutic Decisions
• ACEIs are effective in treating hypertension and/or heart failure.
• ACEIs are more effective in Caucasians because of higher renin levels.
• They are effective as monotherapy in decreasing BP in mild-severe hypertension.
• They are considered first line therapy in hypertension when compelling factors exist but not in uncomplicated hypertension.
• Efficacy is enhanced by other antihypertensive agents including thiazide diuretics and calcium channel blockers.
• ACEIs can cause hyperkalemia. Monitor patients closely when used with a potassium- sparing combination product.
• Shown to be effective in heart failure.
Captopril Analogs
• Mercapto group may interact with food. Foods with high protein content are more likely to decrease absorption of this drug. Give one hour before or 2-3 hours after meals.
• Mercapto group binds to taste buds and giving captopril the highest incidence of taste disturbances. This may contribute to the indirect weight loss seen in patients on captopril because of decreased food intake.
• Large doses of captopril are associated with a higher incidence of skin rash (about 10%) compared to other ACEIs. It is thought to be related to the presence of the mercapto group.
• Captopril undergoes extensive metabolism to a cysteine disulfide which is inactive. This results in a decrease in duration of action necessitating three times a day dosing. This may affect patient compliance.
Enalapril Analogs
• Lacks the mercapto group resulting in a decrease incidence of taste disturbances and allergic reactions.
• Are more potent than the captopril analogs.
• Are in prodrug forms, the presence of the ester yields better oral absorption and increased bioavailability. Can be given orally and once a day which enhances patient compliance.
• Lisinopril has Lysine for the second amino acid. The amino butyl group enhances oral absorption and allows for oral administration despite the lack of an ester.
• The free form is given intravenously for treating hypertensive crisis or for short durations if the patient is unable to take oral medications. It is poorly absorbed orally because of decreased lipophilicity.

benzothiadiazine), a thiazide diuretic. Considering the fact that the patient has hypokalemia, ACEIs may increase potassium by inhibiting the increase in aldosterone, which is helpful and will counter the hypokalemic effects of compound 2. Although both structures 3 and 4 may appear to be possible choices for the patient, structure 3 lacks the critical phenyl ethyl and -NH groups needed for potent activity, while structure 4 has a straight chain carboxylic acid binding moiety rather than the essential cyclic amino acid required to prevent hydrolysis by amidases in vivo.

Prediction of Clinical Activities. Since our goal is to challenge the student to integrate information, think at a higher level, and apply the knowledge clinically, this section is an opportunity to demonstrate that before sitting for course evaluation activities. The learning experiences web page also has a link to SBTE cases and old examinations so that students can practice and hone their skills.

(1) MS is a patient at your pharmacy who is receiving a prescription for captopril (Figure 5). What structurally-based therapeutic advice should be given to MS? Give a one-two sentence SBTE for each.

(2) JJ is a 75-year-old white female who lives in Middle River Nursing Home. She is currently on continuous gastric (G)-tube feedings to help her maintain her weight. She has recently been diagnosed with heart failure. Physician wants to start oral therapy for her heart failure and to administer it via the G-tube. Which of the structures in Figure 5 will not be a good choice to administer to JJ through her feeding tube? Provide a structurally based explanation for your answer.

ASSESSMENT

Our attempts to challenge our students to integrate previous information, think at a higher level, and apply the knowledge to therapeutically relevant situations have been challenging but rewarding. Student performance on course examinations, instructor perceptions of student in-class/online participation, and student perceptions related to the course provide ample evidence that our approach, overall, does ensure the desired outcome of applying basic science knowledge to make therapeutic decisions.

Evidence of students achieving course objectives includes student performance on examinations and

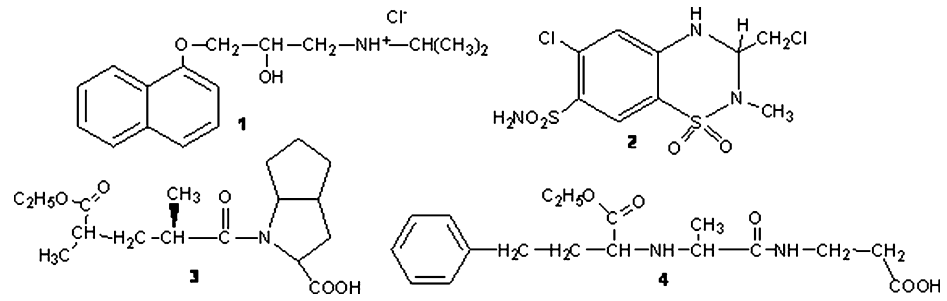

Figure 6. Clinical applications exercise structures.

instructors' perceptions of student participation in in-class and online discussions. Student performance for the academic years 2005-2006 (campus n = 110 and distance n = 60) and 2006-2007 (campus n = 109 and distance n = 49), in which the above approach has been utilized, has shown both campus and distance-education students performing in the 81.4%-86.7% range on all examinations. Performance in the previous 4 years was in the 74.2%-79.4% range. Average class performance (campus and distance) on examination with content on the ACEIs lesson was 83.7% compared to an average of 75.7% in the previous 4 academic years. Although demographics vary between class years and between campus and distance-education students, our admission criteria is set up to select students who are more likely to succeed in their respective education pathway, and consequently, the demographics should not confound the differences seen in test performance.

Examination questions are in essay (20%-30% of an examination) and multiple-choice format and 80%-90% are based on SBTE case studies.[9,11] Students are challenged to answer questions based on recalling critical basic science knowledge, integrating that knowledge with key patient clinical information including: current and past medical history; side effects the patient is experiencing; potential drug-drug and drug-food interactions; and pharmacokinetic parameters, and finally make an appropriate clinical decision for the patient. Student performance on the essay component of the examinations provides evidence of an in-depth understanding of lesson and course content with several students providing what would be considered key answers.

Although the multiple-choice format may not be the best way to evaluate the students, the large class size (160) and the need for a quick turnaround time for examination feedback and results (especially for distance students) made the multiple-choice format component of the examinations a practical approach. In addition, over the last 7 years, the instructor has gained extensive experience in writing that type of question and has attended faculty development workshops both on campus and at national meetings.

Student participation in the interactive in-class and online discussions has also improved over the last 2 years, including the number of students interacting in the in-class/online discussions and the quality of the contributions — another indication of students meeting course objectives. However, participation remains a concern and new strategies are always sought to improve the participation of both student cohorts.

Student perceptions based on course evaluations in the academic years 2005-2006 and 2006-2007 are another indication of how our approach is achieving educational goals. All evaluations were conducted electronically in QuestionMark Perception (Questionnark Co., Norwalk, Conn) and student input remains confidential.

Both campus and distance-education student cohorts (170 in 2005-2006 and 158 in 2006-2007) have shared through formal course evaluations how the knowledge gained helped them better understand the respective topics in pharmacology and to see the "big picture." Major course themes common to both student cohorts included "made you think outside the box" and "helped establish a distinct connection between science and pharmacy practice."

Indications of student learning and their appreciation of the clinical relevance of the knowledge they gained is represented by the significant number of students who stated that they are using the knowledge as pharmacy interns in their employment sites, how they are reviewing package inserts to decipher clinical information about drugs based on the structure, and how they applied some of the knowledge to answer questions from family and friends. This is a welcomed outcome since it shows that the students are envisioning how to use the knowledge in their future practice.

The above perceptions are supported by summative course evaluations from both the campus and distance-education students, with all students (100%) indicating that they somewhat agree or agree that the course

prepared them to think like a health care professional (based on a sliding scale of agree, somewhat agree, neutral, somewhat disagree, and disagree). This was true for both campus and distance-education students in the fall and spring semesters of 2005-2006 and 2006-2007. The 100% agreement was much higher than the average of 75% of students in previous years agreeing with this statement.

A major aspect of transitioning the students to the higher level of thinking and to apply the knowledge to therapeutically relevant situations is the number of course activities that compliment the course goals. The pre-assessment quizzes, lesson handout, taped interactive in-class PowerPoint slide presentations, old examinations, and SBTE exercises were perceived by the 2005-2006 students as highly helpful in providing clinical relevance (93% and 97%, respectively). Similar perceptions were noted by 2006-2007 students. The majority of students also noted that the lesson handout aided student learning, integrating previous information, and transitioning them to think critically. Overall, all the students agreed that the course helped in promoting their clinical reasoning process. This is captured by the following student comments:

> More valuable than I could ever imagine. I feel like a real pharmacist now. I feel like I have a deeper understanding of what drugs actually do and why side effects occur.
>
> I was one of those who had the attitude "why do we have to take this class and learn a whole bunch of structures?" However, I can now see the clinical importance of knowing the drugs from its very core, which is its structure.

DISCUSSION

Despite the positive data based on student performance and instructor and student perceptions, ongoing efforts are expended to ensure that all student issues related to achieving course educational outcomes are addressed on a semester-by-semester basis including the organization and clarity of the lesson handout, the type and order of the lesson activities, the instructional methods for all student cohorts, and the type and format of course evaluations. Gauging student attitude during the semester and making modifications accordingly is also a must to optimize student ability to achieve educational goals.

Our lesson handout follows a logical approach. The organization of the lesson handout transition students to the higher level of thinking required to integrate and analyze patient information to make therapeutic decisions based on the chemical structure of the drug. Both the lesson handouts and the course activities have evolved over the last 13 years the course has been taught. However, with the appropriate preparation and a well thought out approach to achieving their own course objectives, faculty members teaching in the same discipline or other related disciplines should be able to transform their course handouts and plan lesson and course activities to support their educational goals. Seeking input from basic science and clinical faculty members, addressing current and previous students' course concerns, challenging the students to recall and integrate content from other courses, and reviewing primary and secondary clinical literature is very helpful in achieving all of the above.

SUMMARY

The chemical basis of drug action course sequence is a required 2-semester course sequence taught to second-professional year pharmacy students at Creighton University in both the campus and distance-pathways. The course challenges the students to integrate previous content, think critically, and apply the content to therapeutically relevant SBTE cases. The ACEIs drug class was utilized to showcase how students are transitioned through a standardized approach to recall and integrate previous science knowledge, learn and apply ACEIs pharmacophore and SAR knowledge, establish a logical connection between the chemistry of the ACEIs and therapeutics and finally to apply the chemistry knowledge to predict clinical activity and patient outcomes based on clinically relevant case scenarios. In the process, we try to demonstrate the essential role science courses play in helping students build the foundational knowledge, explain the "why" questions, and think at a higher level. As science faculty, it is always critical to challenge ourselves to create more opportunities for all our students to apply the knowledge gained in contexts that prepare them for their future role as pharmacists.

REFERENCES

1. Alsharif NZ, Galt KA, Mehanna A, Chapman R, Ogunbandeniyi AM. Instructional model to teach clinically relevant medicinal chemistry. *Am J Pharm Educ.* 2006;70(4):Article 91.

2. Webster AA, Riggs RM. A quantitative assessment of a medicinal chemistry problem-based learning sequence. *Am J Pharm Educ* 2005;70(4):Article 89.

3. Roche VF, Alsharif NA, Ogunbadeniyi AM. Reinforcing the relevance of medicinal chemistry to the practice of pharmacy through the *Who Wants to Be a Med. Chem. Millionaire* Learning Game. *Am J Pharm Educ.* 2004;68, Article 112.

4. Roche VF, Alsharif NZ. Stayin' alive: advancing medicinal chemistry by enhancing student responsibility for learning. *Am J Pharm Educ.* 2002;66:319-28.

5. Mehanna AS. NSAIDs: chemistry and pharmacological actions. *Am J Pharm Educ.* 2003;67, Article 63.

6. Alsharif NZ, Shara M, Roche VF. Structurally-based therapeutic evaluation (SBTE): An opportunity for curriculum integration and interdisciplinary teaching. *Am J Pharm Educ.* 2001;65:314-23.

7. Dimmock JR. Problem solving learning: applications in medicinal chemistry. *Am J Pharm Educ.* 2000;64:44-9.
8. Abate MA, Meyer-Stout PJ, Stamatakis MK, Gannett PM, Nardi AH. Development and evaluation of computerized problem-based learning cases emphasizing basic sciences concepts. *Am J Pharm Educ.* 2000;64:74-82.
9. Alsharif NZ, Roche VF, Destache C. Teaching medicinal chemistry to meet outcome objectives for pharmacy graduates. *Am J Pharm Educ.* 1999;63:34-40.
10. Harrold MW. Importance of functional group chemistry in the drug selection process: case study. *Am J Pharm Educ.* 1998;62:24-30.
11. Alsharif NZ, Theesen KA, Roche VF. Structurally-based therapeutic evaluation: A therapeutic and practical approach to teaching medicinal chemistry. *Am J Pharm Educ.* 1997;61:55-60.
12. Herrier RN, Jackson TR, Consroe PF. Use of student centered, problem based, clinical case discussions to enhance learning in pharmacology and medicinal chemistry. *Am J Pharm Educ.* 1997;61:441-6.
13. Krathwohl DR, Bloom BS, Masia BB. Taxonomy of Educational Objectives: book 2; affective domain. New York: Longman; 1964.
14. Malone PM, Glynn GF, Stohs SJ. The development and structure of a web-based entry level doctor of pharmacy pathway at Creighton University Medical Center. *Am J Pharm Educ.* 2004;68(2):Article 46.
15. Harrold M. Angiotensin converting enzyme inhibitors, antagonists and calcium channel blockers. In: William DA, Lemke TL, editors *Foye's Principles of Medicinal Chemistry,* 5th ed. Baltimore MD: Lippincott Williams & Wilkins; 2002:454-7.
16. Nogrady T, Weaver DF. Inhibitors of the renin-angiotensin system. In: Nogrady T, Weaver DF, eds. *Medicinal Chemistry: A Molecular and Biomedical Approach.* 3rd ed. Oxford: Oxford University Press; 2005. p. 371-375.
17. Gringauz A. Drugs and the cardiovascular diseases. In: Gringauz A, ed. *Introduction to Medicinal Chemistry: How Drugs Act and Why?* 1st ed. New York: Wiley-VCH, Inc; 1997:450-61.
18. Saseen JJ, Carter BL. Hypertension. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey ML, eds. *Pharmacotherapy: A Pathophysiologic Approach.* 6th ed. New York: McGraw-Hill Companies, Inc; 2005:185-218.
19. Koda-Kimble MA, Young LY, Kradjan WA, Guglielmo BJ, Alldredge BK, Corelli RL. *Applied Therapeutics: The Clinical Use of Drugs,* 8th ed. Baltimore, Maryland: Lippincott Williams & Wilkins; 2004.
20. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42: 1206-52.
21. Furberg CD, Pitt B. Are all angiotensin-converting enzyme inhibitors interchangeable? *J Am College Cardiology.* 2001;37: 1456-60.
22. Ravid D, Lishner M, Lang R, Ravid M. Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and in congestive heart failure. *J Clin Pcol.* 1994;34:1116-20.
23. Thind GS. Angiotensin converting enzyme inhibitors: comparative structure, pharmacokinetics, and pharmacodynamics. *Cardiovascular Drugs and Therapy.* 1990;4:199-206.
24. Zusman RM. Effects of Converting-Enzyme Inhibitors on the Renin-Angiotensin-Aldosterone, Bradykinin, and Arachidonic Acid-Prostaglandin Systems: Correlation of Chemical Structure and Biologic Activity. *Am J Kidney Diseases.* 1987;1:13-23.