The Structurally-Based Therapeutic Evaluation (SBTE) Concept: An Opportunity for Curriculum Integration and Interdisciplinary Teaching

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Curriculum integration has become an important concept in pharmacy education, as it provides a framework for students to apply knowledge from several disciplines and to use this knowledge to solve real-life problems. In the process, students begin to develop critical thinking and problem solving capabilities that they will carry with them into their professional careers. Curriculum integration can be challenging when applied to biomedical, pharmaceutical and clinical sciences, but appropriately modified courses can help students integrate ideas and concepts gained in earlier courses so as to meet specific pharmaceutical care outcomes defined by their institution. Many, including those who instruct in the medicinal chemistry discipline, are actively embracing these concepts and challenges. In two previous papers, we introduced The Structurally Based Therapeutic Evaluation (SBTE) teaching approach in the medicinal chemistry courses at Creighton University. We discussed how this teaching style emphasizes the relevance of medicinal chemistry to the practice of pharmacy and how it can be utilized to meet pharmaceutical care outcomes for pharmacy graduates. In this paper, we will discuss how the SBTE can be used to promote curriculum integration and to foster interdisciplinary teaching.

INTRODUCTION

With the adoption of the pharmaceutical care concept(1,2), pharmacists have become increasingly involved in patient care. Pharmaceutical education has changed accordingly, with increased emphasis on therapeutics, patient assessment and counseling, care plan development and monitoring, communication skills and early practice experiences. In this era of enhanced understanding of the molecular basis of disease, the structure and function of drug receptors, and the chemical mechanisms of communication between cells, biomedical and pharmaceutical sciences content is more critical than ever before. However, there is sometimes less curricular time devoted to these concepts due to the aforementioned expansion of clinically-related content.

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In the face of this curricular dilemma, schools and colleges of pharmacy must encourage faculty in the different disciplines to coordinate their teaching efforts and/or develop interdisciplinary courses and experiences to optimize the knowledge students will gain. In fact, many schools and colleges of pharmacy are currently increasing their emphasis on curriculum integration. A major benefit of integrating content across the curriculum is the opportunity to introduce and reinforce biomedical and pharmaceutical sciences while applying these concepts and principles to the actual practice of the profession. Content integration helps students see how the science and practice of pharmacy come together in a “big picture” of scientifically grounded, evidenced-based pharmaceutical care, and guides them to become critical thinkers and life long learners. Further, when content is integrated across the curriculum, students can continuously focus on the importance of the clinical knowledge they are gaining and how it meets the needs of the society they will serve as health care professionals.

Curriculum integration is of great importance since contemporary pharmacy practice requires a sound foundation in the biomedical, pharmaceutical and clinical sciences. However, there are several potential barriers to curriculum integration including:

- Separation of these curricular areas in ways that reduce the opportunity for content integration (e.g., biomedical sciences in the first professional year, pharmaceutical sciences in the second professional year and clinical sciences in the third professional year);
- Instruction and coordination of biomedical sciences courses (e.g., anatomy, physiology, biochemistry, pathology, microbiology) by faculty external to the pharmacy school;
- Lack of understanding and involvement of faculty from each scientific area in the professional activities (research activities, practice activities) of the other.

To minimize or eliminate these potential barriers to curriculum integration, it is essential that biomedical, pharmaceutical and clinical science faculty actively develop strategies for integrating course content and learning activities, and that the concept of faculty and curricular interdependence is advocated by administration at the department and college levels.

The ultimate goal of curricular integration and interdisciplinary teaching is to create a learning environment in which future health care professionals learn to work together to improve health care delivery, and to better understand the complex and comprehensive nature of disease and drug therapy. One approach that schools can use to promote curricular integration is structured interdisciplinary experiences for students. This has become an important strategy in health care education and practice activities (research activities, practice activities) of the other.

In two previous papers, we introduced The Structurally Based Therapeutic Evaluation (SBTE) teaching approach in the medicinal chemistry courses at Creighton University. We discussed how this teaching style emphasizes the relevance of medicinal chemistry to the practice of pharmacy and how it can be utilized to meet pharmaceutical care outcomes for graduates. In this paper, we will discuss how the SBTE approach can be used to promote curriculum integration and foster interdisciplinary teaching.

### General SBTE Goals

The goals of the SBTE concept include: (i) making chemistry relevant to the practice of pharmacy; (ii) enhancing student interest in the discipline; (iii) helping students apply chemistry to clinically relevant situations; (iv) helping students master many of the professional functions, skills and standards of pharmacy practice as expressed in our Ability-Based Educational Outcomes for Graduates (Appendix A); (v) challenging students and faculty to integrate concepts taught in earlier courses; and (vi) introducing concepts that will be developed in future courses. The SBTE requires students to identify basic structure-activity relationships and physicochemical properties of drug molecules, and then apply seven therapeutic criteria to translate structural knowledge into predicted pharmacological action to solve real-life therapeutic problems and to master professional functions and skills.

### SBTE AND CURRICULUM INTEGRATION

Our two previous papers address SBTE goals 1-4, but another major goal of the SBTE approach is to foster integration of previously learned concepts and principles as well as set the stage for learning yet to come. Curriculum integration utilizing the SBTE approach is made explicit through a formal presentation to the students during the first class session. The integrative process is conducted in a standardized step-wise manner where, for each drug class, students are instructed to sequentially:

1. apply concepts from organic chemistry, biochemistry, anatomy, and pathophysiology to the structure activity relationship (SAR)-based drug decision process,
2. briefly summarize pharmacology concepts,
3. identify clinically relevant therapeutic issues,
4. apply SAR to explain the pharmacology and support therapeutic decisions, and
5. apply SAR to meet pharmaceutical care functions and professional practice skills as expressed in the Ability-Based Educational Outcomes for Pharmacy Graduates document

Students are challenged to apply the process to each drug class discussed, on homework assignments and on examinations. The following cardiovascular example provides a detailed summary of how the SBTE approach offers the opportunity for curriculum integration. The summary is based on the standardized five-step approach described above, and utilizes four drug classes, beta-adrenergic receptor blockers, diuretics, angiotensin converting enzyme inhibitors (ACE-IIs) and angiotensin antagonists.

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Table I. Summary of major principles and concepts

<table>
<thead>
<tr>
<th>Course</th>
<th>Principles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic Chemistry</td>
<td>Log P (distribution); Functional groups; properties and stability (solubility, rates of metabolism, bioactivation); Intermolecular interactions (receptor affinity); Resonance and inductive character of groups.</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Renin-angiotensin biosynthetic pathway; properties of cholesterol and lipids, clinical biochemistry (including renal and hepatic function tests, electrolytes, lipid profile)</td>
</tr>
<tr>
<td>Anatomy &amp; Physio-</td>
<td>Renal anatomy and physiology (nephron function, renal handling of specific anions and cations); pulmonary and cardiovascular anatomy and physiology, blood brain barrier.</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Asthma, hypertension, hyperlipidemia, atherosclerosis, myocardial infarction, congestive heart failure</td>
</tr>
</tbody>
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Cardiovascular Example
NA, a 55-year-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 four-year history of hypertension that has been poorly controlled with structure 1 and structure 2. 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) = 102 ml/min (90-120), total cholesterol 280 mg/dl (< 200 mg/dl). NA has a history of noncompliance.

STEP 1: Application of Basic Principles
Table I summarizes some of the major principles and concepts from the basic sciences and the biomedical sciences that students must integrate into their overall understanding of how to address the therapeutic needs of NA. The disciplines and the concepts listed in Table I are not all-inclusive. Students may add other disciplines and concepts that they think are necessary for their overall understanding of these drugs, and are encouraged to review books, medical literature and their notes from previous courses to have a good understanding of the related principles and concepts. For early lessons students are provided with specific page numbers in the required textbooks from previous courses, and are encouraged to do the same independently for later lessons.

With our switch to a web-facilitated curriculum, curriculum integration will be achieved in a more comprehensive manner since faculty and students will be able to link to content on the web pages of both previous and future courses to emphasize specific concepts. To promote web-facilitated content integration, a voluntary (extra credit) assignment gave students the opportunity to identify the “missing link” for key words and concepts in any of the drug topics discussed, and many students participated. Recognizing that the quality of web sites that provide drug and/or medical information runs the gamut from abysmal (or dangerous) to excellent, students participating in this exercise are instructed to verify the authenticity, reliability and quality of the health-related information they find before submitting the site for evaluation by the instructors. Through this extra credit exercise, students have identified several sites that have enhanced the utility of our course web site. For example, to compliment the diuretics lectures, one student contributed the site http://oak.cats.ohiou.edu/~henleyb/OsmonoTrans/sld008.htm, which explains the mechanism of action of the different classes of diuretics and provides an excellent diagram that clearly show the site of action and the effects on electrolyte movement. Other sites identified by students included web pages that review the anatomy of the kidney, a review of disease states that may require diuretic therapy, a discussion on creatinine, a review of loop diuretic ototoxicity, a medical dictionary and a website for the Kidney Foundation. Figure 1 provides other websites identified by students that were linked to specific terms and concepts in the course notes to elaborate on the course content. The following are examples of how understanding and integration of basic and biomedical sciences principles should be applied to provide pharmaceutical care to NA. The italicized statements and associated questions are the same as those given to, and asked of, the students. All relevant structures are provided in Figure 2.

Structure 1 may have contributed to the CNS side effects NA is experiencing. Give a SBTE to explain these adverse drug reactions. [organic chemistry, anatomy, physiology, pharmacokinetics]

Students understand the anatomical structure and physiology function of the blood brain barrier, having learned in previous anatomy and physiology coursework of the network of tightly connected endothelial cells and their exclusionary impact on all hydrophilic molecules(14). Structure 1, propranolol, is readily recognized by its aryloxypropanolamine structure as a beta-blocker. The contributions to lipophilicity of the various functional groups and the impact of overall lipophilic/hydrophilic character on membrane penetration and partition (log P) are two important organic chemistry concepts that students should apply in order to provide the SBTE. Although the relationship between the extent of CNS side effects and the log P of beta blockers has never been clearly substantiated, it is well accepted that the higher incidence of CNS side effects exhibited by propranolol is due to its high lipophilicity which allows more extensive penetration through the blood brain barrier(15-17).

Would switching from structure 1 to structure 3 be a good therapeutic decision? Provide a SBTE for your answer, [organic chemistry, anatomy, pharmacokinetics]

In general, drugs must exhibit a balance between hydrophilicity and lipophilicity to be able to effectively traverse the biological barriers separating the sites of drug administration, action, metabolism and excretion. This is taken into account when chemical modification of a given agent to improve the therapeutic efficacy is considered. Students can readily see that structure 3 (nadolol) is a reduced tetrahydrolipophenylene analog of propranolol. While the reduction of an
aromatic ring is a lipophilic structural change, the addition of the two polar hydroxyl groups significantly decreases nadolol’s overall lipophilic nature and, therefore, its CNS penetration(18). Also, the decreased lipophilicity minimizes first pass metabolism and, as a result, the duration of action is increased.

Consequently, nadolol is dosed once a day. On the other hand, lipophilic propranolol undergoes extensive first pass metabolism to an active 4-OH metabolite and inactive N-dealkylated metabolites. This results in a decrease in the duration of action, and bid or tid dosing is common. The qd dosing combined with a decreased potential for CNS side effects makes nadolol a better therapeutic choice considering NA’s history of non-compliance and the CNS effects he is experiencing.

Would switching from structure 1 to structure 4 be a good therapeutic decision? Provide a SBTE for your answer, [anatomy, biochemistry, organic chemistry, physiology]

Students recognize from structure that compound 4 is an enalapril analog with ACE-inhibiting activity. From their required anatomy and physiology readings(19), students are aware that the major site of production of the vasoconstricting peptide, angiotensin II (AT-II), is the blood vessels. The physiological responses to this substrate include an increase in systemic vascular resistance, increase blood pressure (after load), an increase in pulmonary capillary wedge pressure (preload), all leading to decreases in cardiac output and perfusion of vital organs (heart, kidney). Since ACE-Is prevent the formation of
AT-II, these adverse cardiovascular sequella will be prevented. The biochemical and physiological characteristic of ACE-Is make this class of drugs a viable choice for treatment of hypertension. From their study of intermolecular interactions in organic chemistry and their understanding of the structure of the ACE enzyme from biochemistry and physiology, students recognize that ACE-Is have the structural features needed to bind electrostatically to the catalytic and zinc-binding sites of the enzyme (Figure 3). The two amino acid distance between the two ionizable sites is critical, and optimal in the marketed ACE-Is, such as structure 3. Students should review the above concepts to fully understand the pharmacological activity and therapeutic utilization of ACE-Is for the treatment of hypertension. Linking the students to the websites of previously completed biomedical science courses can facilitate a focused review of key concepts. In addition, http://www.aafp.org/htdigsearch/htsearch has more detailed information regarding the therapeutic use of ACE-Is and is recommended reading for students.

STEP 2: Summary of Pharmacology Concepts

Concepts learned in pharmacology allow students to understand the mechanism of action of all compounds discussed in this case. Selectivity for $\beta_1$ and $\beta_2$ receptors, first pass metabolism, and the major side effects of the above drug classes (e.g., ototoxicity with loop diuretics, steroid-like effects with aldosterone antagonists, hyperkalemia with potassium-sparing diuretics and ACE-Is, and hypokalemia with thiazide and loop diuretics) are also important issues that are addressed in pharmacology-related coursework. Students are expected to review pertinent pharmacology concepts and other related principles to better their understanding of the chemistry of this class of drugs.

Pharmacology is offered concurrently but independently from medicinal chemistry, and the difference in credit hours assignment (10 vs. 5, respectively) precludes an exact sequencing of topics. If students have not formally studied a medicinal chemistry topic in their pharmacology course, a brief overview of key concepts is presented in class, but students are still expected to read ahead on their own.

Three months later, NA was complaining of a productive cough with increasing frequency and duration. He also exhibited increasing dyspnea on exertion. NA was diagnosed with chronic bronchitis. The physician wants to continue beta-blocker therapy for the control of NA’s hypertension. Which $\beta$-adrenergic antagonist [3, 5, 6, or 7] would be considered a “safer” alternative to structure 1 to control NA’s hypertension? [anatomy, pathophysiology, pharmacology, organic chemistry]

Students have studied the definition of the term an “agonist,” “antagonist,” “selectivity” and “intrinsic sympathomimetic activity” in their introductory pharmacology course. As students in the early years of their professional curriculum still tend to view concepts in an “all or none” manner, they are reminded that drug selectivity is a relative term and that at higher doses, selectivity is diminished. An understanding of the anatomy of the lungs, the location and density of receptors and their subtypes, and the pathophysiology of pulmonary disease including asthma, chronic obstructive pulmonary disease (COPD) and bronchitis are also relevant to this question. Patients with bronchitis, COPD or asthma are more susceptible to bronchoconstriction. Therefore, drugs that cause bronchoconstriction are contraindicated.

As a result of this review of biomedical and pharmacological science principles, students are aware of the need to choose a $\beta$-adrenergic antagonist with $\beta_1$-selectivity, since blocking of $\beta_2$ sites will result in bronchoconstriction. For $\beta_1$ selectivity, a $\beta$-adrenergic antagonist should contain a p-substituted aryloxypropanolamine pharmacophore. Therefore, structure 7 (betaxolol) would be a good choice for NA, however the lowest effective dose should be used. All other beta antagonist structures (e.g., 3 and 5), lacking this essential structural requirement, are non-selective and would block the $\beta_2$ receptor, worsening NA’s pulmonary condition. Structure 6, (pin dolol), contains an indol ring which is known to contribute to its intrinsic sympathomimetic activity, possibly through a hydrogen bonding interaction between the m-heteroatom and SER204 of $\beta$ receptor residue. Its partial agonistic activity makes it safer to use than propranolol, but not as safe as betaxolol. NA should be advised to contact his physician if he is experiencing any shortness of breath or if any of the CNS side effects he experienced on propranolol return. The students often appropriately recognize that switching to a different class of antihypertensive drugs would be the safest option of all.

STEP 3: Clinically Relevant Therapeutic Issues

At Creighton University, the medicinal chemistry courses are offered in the second year of the professional program, while the capstone therapeutics courses are offered in the third year. Therefore, when enrolled in the medicinal chemistry course sequence, it is essential that students are familiarized with clinically relevant therapeutic issues and have a clear understanding of how to apply them to solve the therapeutic needs of patients. During the in-class sessions, clinically relevant issues are emphasized and are also summarized in the students’ lecture handout.

Table II summarizes some of the most clinically relevant therapeutic issues for the case in question. The list identifies guidelines for therapeutic decisions that can be explained by the structure and, therefore, a thorough understanding of the

### Table II. Summary of the clinically relevant therapeutic issues

- General therapeutic guidelines for treatment of hypertension and congestive heart failure (e.g., monotherapy and combination therapy)
- Beta blockers with intrinsic sympathomimetic and alpha blocking activity are lipid neutral
- Beta blockers with high lipophilic character have an increased incidence of CNS side effects
- Thiazides are often the most effective antihypertensive diuretics, especially in African-Americans.
- ACE-Is are often the most effective antihypertensive agents in Caucasians
- Thiazide diuretics are ineffective at Clcr < 35 ml/min
- Loop diuretics are primarily used for the treatment of pulmonary edema and in possibly treating hypertension at Clcr < 35 ml/min
- Spironolactone is the drug of choice to restore electrolyte balance in hyperaldosteronism/hepatic cirrhosis
- A potentially significant drug-drug interaction with lithium is possible following long-term thiazide therapy
- Highly lipophilic beta blockers exacerbate the clinical manifestations of depression in patients with that disorder.
structure activity relationship (SAR) is essential to make appropriate therapeutic decisions. The therapeutic guidelines may be expanded based on new literature findings by either the professor or from student research. Input from the clinical faculty should be sought on major clinical decisions that could be emphasized in the medicinal chemistry courses, keeping in mind the emphasis on the SAR and how it explains specific therapeutic decisions.

With respect to the clinical scenario involving NA, students are provided with the following clinically relevant information:

- general treatment guidelines for hypertension including life-style modifications vs. initiation of drug therapy,
- the routine use of diuretics, beta blockers and ACE-Is as initial therapy,
- racial or ethnic influences on sensitivity to therapy and their impact on drug choice,
- the switch from one class to another is most commonly based on troublesome side effects or on lack of response to a drug agent, in which case combination therapy may be indicated.

Once informed of the treatment guidelines, students are expected to apply their knowledge of SAR to the treatment problem at hand. For example, they could confidently recommend not using a highly lipophilic beta blocker in patient with depression, a disease characterized by insufficient stimulation of beta and/or serotonin receptors, modifying the dose of lithium in a patient with manic-depressive disorder following long-term thiazide therapy to prevent toxicity from the increased reabsorption of lithium, and using β2 selective beta blockers in a hypertensive patient with a history of hyperlipidemia, as this pharmacophore does not decrease HDL or increase triglycerides.

**STEP 4: Applying SAR to Explain Pharmacology and Support Therapeutic Decisions**

The emphasis in our courses is on how a thorough understanding of drug structure, and all the clinically relevant information it provides, facilitates the making of wise therapeutic decisions. The foundational information presented by the instructor should be thorough and include a complete discussion of the SAR. To gain the most from the medicinal chemistry experience, students should minimally be expected to read their medicinal chemistry course notes and text(s), but also encouraged (and rewarded) for bringing current information on SAR and molecular mechanism from the primary literature to the attention of the class. Examples of how to apply SAR to explain drug pharmacology and support therapeutic decisions are included in the notes and discussed during the class sessions. Homework assignments, concept tests(20) and other active learning strategies, essay examinations and in-class case presentations by student groups are some of the methods that we have utilized to provide students with application experience. Clinical literature and many therapeutic texts also contain examples of how basic SAR impact therapeutic decisions. Some of the resources we have found most useful are listed in Appendix B. Many of these texts and journals provide cases, information that reinforces relevant concepts in anatomy, physiology and pathology, and clinical information that can be modified to facilitate the students’ understanding of how to utilize the SAR to explain therapeutics realities of all classes of drugs(14-19,21-23).

In the current case, students were referred to the text utilized for the therapeutics courses, in which a step-by-step approach is described for the treatment of hypertension(24). They are provided with a summary of the treatment algorithm and are encouraged to read the assigned section of this text, and then challenged to make appropriate therapeutic decisions through the integration of SAR with the treatment algorithm for hypertension, as exemplified by the following scenario.

Despite attempts to control his hypertension with combination therapy, NA is not being adequately maintained on structures 2 and 7, and the physician wants to change diuretic therapy. Would substitution of structure 8 for structure 2 be a good therapeutic decision? [organic chemistry, physiology, pharmacology, therapeutics, medicinal chemistry]

Structure 2 is a benzothiadiazine structure substituted for high potency with a C4 methyl group, and lipophilic and electron withdrawing functional groups at C1 and C6, respectively. Thiazide diuretics are commonly used in combination with beta-blockers for treatment of hypertension. While potentially useful in patients of all ethnic and racial backgrounds, they are deemed particularly effective in African-American populations, where low renin levels are more commonly observed. In addition, structure 2 may be causing NA’s hypokalemia, since thiazides act at the proximal portion of the distal tubule resulting in increased potassium excretion. Particularly because of the adverse effect of potassium depletion, but also because of inadequate response, structure 2 should be replaced with another class of diuretics.

Structure 8 (furosemide) is recognized by structure as a sulfamylbenzoic acid derivative, and a SAR analysis confirms the presence of the potency-enhancing lipophilic group at C4 and C2 substituent. From physiology and pharmacology coursework, students recognize that, in contrast to the thiazides, this class of loop or high ceiling diuretics acts at the level of the thick ascending limb of the loop of Henle, inhibiting a larger amount of sodium reabsorption. Applying this information to the clinic, furosemide is expected to be effective in the treatment of edema and pulmonary edema, however, it is reserved for hypertensive patients with significantly impaired renal function (Clcr< 35 ml/min.) due to the enhanced potency compared to thiazides like 2. As this loop diuretic does not modify arteriolar tone to the same extent as the thiazide diuretics, it is not used for treatment of hypertension in patients with normal kidney function (recall that NA’s Clcr is =104 ml/min.) and would, therefore, be an inappropriate choice for NA.

**Would replacing structure 2 with structure 9 be appropriate? [physiology, pharmacology, organic chemistry, therapeutics, medicinal chemistry]**

The cyclopentanoperhydrophenanthrene parent structure of compound 9 identifies it as a diuretic that acts through the antagonism of the mineralocorticoid aldosterone. An SAR analysis reveals that it has a similar structure to aldosterone, but it lacks the C17–ketol and the C18–formyl groups that provide potent mineralocorticoid activity to the endogenous hormone. Rather, structure 9 antagonizes the effects of this antidiuretic hormone at the level of the distal collecting duct, preventing the conversion of the aldosterone receptor from its
compounds that function as aldosterone antagonists would have been a good choice to add to his original regimen to prevent the hypokalemic effect of structure 2. However, by itself or in combination with the β-antagonist 7, it may only produce a modest reduction in blood pressure. Further, although it is a good potassium-sparing diuretic, the steroidal structure could induce androgenic side effects (e.g., gynecomastia, decreased libido) that could be problematic in male patients.

Would replacing structure 2 with structure 10 be a sound therapeutic choice? If so, could this compound be given orally? [biochemistry, pharmacology, therapeutics, medicinal chemistry]

Knowledge of amino acid structure from biochemistry allows students to recognize that structure 10 is the lysine analog of enalaprilat, the active component of the ACE-I enalapril. It has all the required structural features for binding to, and inhibition of, ACE as discussed above and shown in Figure 3. An SAR analysis documents the lack of prodrug-forming ester groups on the essential carboxylic moieties, and students recognize that the drug is active as administered. Compound 10 has two ionizable carboxylate groups (pKa values of 1.7 and 3.3)(24) and two potentially cationic amino groups (pKa values of 7.0 and 11.1)(24), and Zwitterionic forms are anticipated at pH 7.4. Despite their charged state, some flexible Zwitterionic molecules can experience polarity-attenuating charge neutralization from intramolecular electrostatic interaction(25). However, compound 10 is the most hydrophilic of the ACE inhibitors(26). It has a high oral bioavailability that is believed due to carrier-mediated transport across gastrointestinal membranes(27). From pharmacology, students know that ACE-I are effective in all stages of hypertension especially in patients with high renin. Since NA is a white male and may be assumed to have relatively high levels of this hypertensive protein, an ACE-I is a reasonable therapeutic choice. Furthermore, students have learned in pharmacology that ACE-Is inhibit aldosterone release, resulting in increased potassium retention. They are then prepared to predict that 9 would have counteracted the hypokalemia NA is experiencing from the thiazide therapy, although potassium loss should no longer be a problem since 2 was eliminated from NA’s regimen. Thinking clinically, they should advise that NA’s serum potassium continue to be monitored, especially early in therapy, to ensure that the addition of this potassium-sparing diuretic does not cause hyperkalemia.

Could structure 11 be used orally in combination with NA’s current therapy? If so, would convenient qd dosing be possible? [biochemistry, pharmacology, therapeutics, medicinal chemistry]

Compound 11 is recognized by structure as the angiotensin II antagonist losartan, a nonpeptide antagonist of one of the AT1 subtype of the angiotensin II receptors. Losartan is effective as monotherapy or in combination with other antihypertensive agents (diuretics in particular) in mild-moderate hypertension. From their study of SAR, students know that the biphenyl ring system must be attached directly to a five-membered heterocycle for activity to be realized. They further recognize that the lack of a functional group between the two phenyl rings is important for oral activity. Knowledge of drug metabolism from biochemistry, pharmacology and medicinal chemistry permits the prediction of the CYP450-mediated bioconversion of the primary alcohol to a carboxylic acid metabolite that is 10-40 times more potent than the parent structure. The formation of an active metabolite ensures a long t1/2 allowing for qd dosing which would be beneficial in light of NA’s tendency towards noncompliance. As losartan can be used as monotherapy or in combination with other antihypertensives, it may potentially be added to NA’s drug therapy.

The SAR of the major classes of antihypertensive agents discussed above may also help explain the advantages and disadvantages of the therapeutic use of each drug class based on the clinical presentation of the patient. The following case exemplifies this.

VR, a white female with a history of chronic congestive heart failure is admitted to the hospital complaining of increasing shortness of breath (SOB) and an 8 kg weight gain. Four months before, she noted ankle edema and the onset of dyspnea on exertion after climbing even a single flight of stairs. Since that time, her symptoms have progressively worsened with signs of pulmonary edema. Her Clv is 25ml/min. VR has been treated with structure 12. Would the following be good therapeutic changes to the above drug therapy?

1. Add structure 2 to the regimen [physiology, therapeutics, medicinal chemistry]

   Algorithms that outline a stepwise approach to the treatment of chronic heart failure are available in commonly utilized therapeutic textbooks(28). In general, ACE-Is such as 12 are considered the drug treatment of choice. ACE-Is improve heart failure by reducing the workload of the heart secondary to a reduction in both arterial (afterload) and venous (preload) resistance. Upon presentation of symptoms such as those experienced by VR, a diuretic should be added. Structure 2, as discussed above, is a thiazide diuretic appropriately substituted for high potency within this therapeutic class. Diuretic therapy is important to counter the excessive sodium and water retention and other symptoms of pulmonary edema. However, as a thiazide diuretic, structure 2 mainly acts on the distal convoluted tubule affecting only 5-8 percent of filtered sodium. Therefore, it is considered a relatively weak diuretic and is, therefore, infrequently used in heart failure. It would not be appropriate for combination therapy with an ACE-I in this patient.

2. Administer a large IV dose of structure 8. [therapeutics, medicinal chemistry]

   As noted in the previous SAR discussion, structure 8 (furosemide) is a sulfamylbenzoic acid diuretic. When given intravenously, it increases venous capacitance independently of diuretic effect and produces a rapid improvement in pulmonary edema and is used therapeutically for treatment of edema or pulmonary edema. Also, the effectiveness of loop diuretics such as 8 is maintained in kidney dysfunction (recall VR’s Clv is only 25 ml/min.). Caution should be taken in giving large doses of furosemide intra-
venously in patients with renal dysfunction, as this may result in ototoxicity, exemplified by tinnitus and/or hearing loss few days after the therapy. The mechanism involved is hypothesized to be due to accumulation of anionic drug in the inner ear, which causes changes in the physiochemical properties of the fluid and adversely affects sound transmission.

**STEP 5: Meet Specific Outcome Objectives**

In our previous paper(13) we discussed how the SBTE concept meets the specific outcome objectives for our pharmacy students. These outcome objectives are considered critical to the development of a competent practitioner who is proficient in all of the essential skills needed to render pharmaceutical care. Many of the above examples meet outcome objectives for instilling critical thinking, life long learning, and therapeutic decision making skills in students. The following is an additional example of how the SBTE approach can reinforce specific ability-based outcomes:

**Counsel Patients**

MS is a patient at your pharmacy who is receiving a prescription for structure 12. What structurally-based therapeutic advice should be given to MS. Give a one-two sentence SBTE for each [communication skills, pharmacology, therapeutics, medicinal chemistry]

Structure 12 is an ACE-I (captopril) as analyzed from the pharmacophore. The sulfhydryl moiety is important to the enzyme inhibiting action of this drug, as it serves as the anchoring group to the zinc-binding site, but it is also responsible for many of the adverse effects commonly observed with this agent. MS should be asked about known or suspected drug allergies since cross allergenicity exists with other drugs that contain a thiol group (e.g., propylthiouracil). MS should also be advised that he may experience taste disturbance due to the reaction of the sulfhydryl group with CYS residues of taste bud proteins. Since this coupling reaction can also occur with proteins found in food, MS should be told to take captopril one hour before meals in order to minimize disturbances in absorption. MS should be advised to call his physician if he experiences a rash, as the sulfhydryl group can form allergenic complexes that manifest as skin irritation. MS should be told that he may experience a dry cough secondary to drug-induced increases in bradykinin in the lungs. Finally, MS should be advised to be alert to the signs and symptoms of hyperkalemia since ACE-Is may increase serum potassium secondary to a decrease in aldosterone.

**DISCUSSION**

A common approach to interdisciplinary teaching brings faculty members from different disciplines together to teach, either in blocks or in a truly integrated fashion, their discipline’s approach to the understanding of a particular topic. While this can be very effective if the faculty involved are truly a teaching team (rather than a sequence of individuals talking independently about a given topic), there are drawbacks. Truly integrated teaching is very time intensive since, when done appropriately, faculty meet regularly outside of class to plan the integrated experience and attend class both to present content and to participate in discussions when their teammates are presenting. Some faculty may feel threatened by the loss of control over the subject matter or the allotment of time within courses they had previously considered their personal domain. If faculty can overcome these barriers, the learning experience for students can be significantly enriched, and the learning environment stimulating for all concerned. If the barriers cannot be overcome, the learning experience and environment can be wrought with frustration for students and faculty alike.

An alternative approach to the ideal of a truly integrated curriculum is for each faculty member to incorporate in their courses learning activities that require reinforcement and integration of previously learned content. In medicinal chemistry courses, the SBTE integration exercise is an effective way to help students couple the knowledge gained from previous biomedical and pharmaceutical science coursework with their evolving awareness of drug chemistry and therapeutic principles to gain a firmer understanding of how all of it works together to explain and predict drug action. Full class discussions during the lecture period further challenge students to integrate information, as does their participation in required group homework assignments based on SBTE and case study exercises similar to the examples provided above.

Even in the absence of an integrative teaching partnership, faculty can enhance the learning experience of students in their courses by establishing productive professional relationships with those teaching other components of the curriculum. Reviewing lecture notes and handouts provided to students in other biomedical or pharmaceutical science courses will help faculty members build on concepts learned in those courses, and keep students from learning in isolation as they begin to see how one discipline’s knowledge links to another’s. Clinical relevance can be introduced and reinforced by reviewing therapeutics texts and the clinical literature in addition to biomedical and pharmaceutical science texts and literature, and by talking with practice faculty about how the concepts being discussed in the pharmaceutical science classroom actually play out in the clinic. Further, medicinal chemists can talk with clinical faculty about important therapeutic concepts they’d like to see introduced in the medicinal chemistry courses, and share important chemistry-related concepts and strategies for incorporating those concepts into the case studies utilized in therapeutics and other clinically based courses.

Curriculum integration facilitated by individual faculty is made easier when those faculty have expertise in both the science and the practice of the profession. However, schools and colleges are finding themselves in a “seller’s market” with regard to faculty availability, and cannot always afford to wait for the ideal, dual-educated faculty member before filling vacant positions. The shortage of qualified faculty is being keenly felt by established schools and colleges, and is only going to intensify as new schools of pharmacy are established. For all of these reasons, faculty should be actively encouraging PharmD students with a talent for the pharmaceutical sciences to obtain a PhD and return to establish careers in the academy. By receiving advanced education, future educators will be better able to bridge the gap between the clinical and pharmaceutical sciences across the curriculum and, through role-modeling critical thinking and a desire for lifelong learning, better prepare the next generation of pharmacists for a scientifically grounded practice.

**CONCLUSIONS**

Content integration and interdisciplinary teaching are impor-
tant curricular goals in the education of pharmacy students. To be responsible in our charge to educate professionals who will serve society throughout their careers, all faculty must ensure that their students master essential knowledge integration skills and recognize how to comprehensively think through problems to promote patient welfare. Medicinal chemistry courses that utilize the SBTE approach have a built-in vehicle to promote the integration of content in the biomedical, pharmaceutical and clinical sciences. Such integration can stimulate communication, cooperation and collaboration among faculty of all disciplines, as well as demonstrate the practical relevance of medicinal chemistry to both students and colleagues.

Planning for meaningful learning with an emphasis on content integration across all disciplines requires an investment of time that some faculty may be hesitant to make, especially prior to promotion and tenure review, due to a perceived negative impact on scholarly productivity or a concern that integration might diminish the perceived importance of their discipline in the minds of their students. Given the positive impact of content integration on learning (31-37), however, incentives must be created for faculty who are willing to invest the time and effort in the integration of content from other disciplines into their courses. In addition to salary considerations, incentives could include active support in bids for promotion and/or tenure, support for attendance at education-based meetings and seminars, and recognition through institutional teaching awards programs.

In summary, content integration across the pharmacy curriculum and interdisciplinary teaching by pharmacy faculty are worthy educational goals, and can be accomplished by:

- explicitly incorporating and reinforcing concepts from other courses while introducing students to concepts they will experience in future courses,
- reviewing texts, lecture notes and handouts from other courses,
- proactively communicating with faculty colleagues teaching other courses in the curriculum that address common topics, appropriately utilizing technology, and encouraging PharmD students to obtain advanced education at the PhD level in a biomedical, pharmaceutical or clinical science discipline and pursue academic careers.

References

(27) Ranadive, S.A., Chen, A.S. and Sera juddin, A.T., “Relative lipohilicities of propranolol, acebutolol, and sotalol,” in Pharmacokinetic behavior of cetirizine, a zwitterionic HI-receptor antag-
(29) Ranadive, S.A., Chen, A.S. and Sera juddin, A.T., “Relative lipohilicities and structural-pharmacological considerations of various angiotensin-
APPENDIX A. ABILITY-BASED EDUCATIONAL OUTCOMES FOR PHARMACY GRADUATES

1. Pharmaceutical Care - The student shall develop pharmaceutical care plans that maximize the patient's response to drug therapy and prevent or resolve drug-related problems. The student shall appropriately document the implementation of and outcomes related to the care plan. The pharmaceutical care plan shall include medical devices, as needed, and educational information, e.g., nutrition, lifestyle, etc., intended to promote general health and prevent or minimize disease progression.

a. Patient Assessment — The student shall contribute to the database of information about the patient by: (i) performing a medication history, review of systems, and physical assessment; (ii) recommending and interpreting laboratory tests; (iii) assessing medical, psychosocial, behavioral, and economic status; and (iv) identifying potential drug-related problems.

b. Drug Therapy Evaluation — The student shall assess and monitor the patient's drug therapy, including a consideration of the chemical, pharmaceutical, pharmacokinetic, and pharmacological characteristics of the administered medications.

c. Pharmacotherapy Decision-Making — The student shall make pharmacotherapy decisions and support those decisions based on knowledge of biomedical, pharmaceutical, administrative, and clinical sciences. The student shall recommend patient use of prescription and non-prescription medications, as well as non-drug therapy.

d. Medication Preparation, Distribution, and Administration — The student shall compound and/or dispense drug products consistent with patient needs and in harmony with the law. The student shall demonstrate the ability to accurately interpret the prescription, select the appropriate dosage form, route and method of administration, and appropriately package and label the product. The student shall demonstrate the ability to administer medications, when appropriate.

e. Systems Management — The student shall use and evaluate acquisition, inventory control and distribution systems, while documenting and maintaining quality. The student shall plan, organize, direct, and control pharmaceutical care systems and human, material, and financial resources, utilizing management theories and information technology.

2. General Education Outcomes
a. Communication Skills — The student shall read, write, speak, listen and use multimedia to communicate effectively. The student shall counsel and educate patients, as well as communicate with other healthcare professionals.

b. Critical Thinking — The student shall acquire, comprehend, apply, analyze, synthesize, and evaluate information. The student shall integrate these abilities to identify, resolve, and prevent problems and make appropriate decisions. The student shall understand the research process.

c. Professional Ethics and Responsibility — The student shall represent the profession in an ethical manner. The student shall embody the responsibilities of pharmacists.

d. Social Interaction, Citizenship, Leadership, Professionalism — The student shall demonstrate appropriate interpersonal behaviors. The student shall provide service to the profession, as well as the community. The student shall be proactive in collaborating with other health care professionals.

e. Life-long Learning — The student shall continuously strive to expand one's knowledge to maintain professional competence.

f. Information Management — The student shall apply technology to pharmacy practice and science. The student shall demonstrate the ability to interpret and evaluate data for the purpose of assessing the suitability, accuracy, and reliability of information from reference sources.

*The pharmaceutical care plan shall include subjective and objective patient information, an assessment of that information, and a plan to resolve and monitor any drug-related problems that were identified.

*Pharmacotherapy decisions determine what, why, when, where, and how drug therapy is provided. The making of pharmacotherapy decisions is the foremost expression of the professional knowledge, responsibility and authority of pharmacists.

APPENDIX B. USEFUL RESOURCES ON THE POSITIVE IMPACT OF SAR/DRUG CHARACTERISTICS ON THERAPEUTIC DECISION-MAKING

Journals
American Journal of Health-Systems Pharmacy
Journal of Clinical Pharmacology
American Journal of Medical Education
Journal of Medicinal Chemistry
American Journal of Pharmaceutical Education
Annals of Pharmacotherapy
Pharmacotherapy
Drugs
Pharmacology and Therapeutics
Journal of American Medical Association
Science

Books
Currie, B.L., Roche, V.F and Zito, S.W. Medicinal Chemistry Case Study Workbook. (1st. ed.) Williams and Wilkins, Philadelphia PA (1996).