Discussion-Based Instruction in Drug Metabolism

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A flexible strategy for large class instruction in drug metabolism is described, which was derived from the SQ3R (survey, question, read, review, recite) method. Students were asked to prepare and discuss answers to fact-oriented study questions addressing fundamentals covered in a reference source (a textbook chapter on drug metabolism). This was followed up by regular evaluation of in-class student responses (written and oral) to “higher order” review questions. Using this discussion-based approach, sustained improvement in class averages on drug metabolism exams over the past four years was seen, compared to those made in the seven previous years when traditional instruction was used. Student interest in drug metabolism, and preference for the style by which it was presented, were generally ranked as high or higher than other less chemistry intensive parts of the course which were covered as lectures. Thus, this discussion-based method may be applicable when improvement in student performance and assessment are sought in undergraduate medicinal chemistry instruction.

INTRODUCTION

First-year undergraduate students in this College receive a course in Introductory Medicinal Chemistry as a prerequisite to later courses dealing with specific classes of pharmaceuticals. Currently, this course is taught once per academic year to 100-125 students. There are instructional modules on principles of drug design/drug action, pharmaceutical analysis, and inorganic medicinal chemistry. But the most significant module, which in some years has comprised about 50 percent of the course content, is on drug metabolism. This is also the part of the course which is the most challenging for the students, as indicated initially by performance on examinations, and in later years by growing student dissatisfaction shared not just with the instructor (PCR), but occasionally with others perceived to have influence within this College. Thus, several years ago it became mandatory to define the problem of mutually unsatisfactory student performance in drug biotransformation. Review of student evaluation responses and comments indicated the problem to center on content and style of delivery of the subject matter, which relied mainly on the traditional lecture method. However, careful appraisal of lecture materials [and examination questions] indicated the problem was not associated with content. Indeed, thorough refinement and regular updating, based on extensive classroom input over the years, had produced lecture notes and supplementary materials that were clear and concise. Thus, it was determined that a more central issue needed to be addressed. This paper describes my approach to development of a discussion-based style of coverage of drug biotransformation in Introductory Medicinal Chemistry. The objectives were to improve student performance, and perception of value, regarding drug metabolism.

Definition of the Problem. The lecture method of instruction is a time-honored way of delivering a large amount of information in a structured way to a large number of students. College students are expected to develop the ability to recognize and record salient information presented during the course of a lecture, a skill that has diverse, important applications in our culture. Most of us like this method because it was familiar to us. However, it has some serious shortcomings and restrictions.

In recent years, it has become clear that performance and attitude may be adversely affected by over reliance on traditional methods of instruction. Several papers from a recent symposium addressing problems with lecture-based instruction were noteworthy in this regard. Results of one study questioned whether the lecture method has a significant role in development of higher order cognitive skills (conceptualization)(1). An ominous conclusion, from a systematic study involving general chemistry students, indicated that class attendance in lectures was not a significant factor in exam performance(2). Finally, the ability of lecture-based instruction to motivate students was challenged (3). Clearly, consideration of student response to lecture presentations was needed in order to pinpoint the reason(s) for my students’ performance and motivation problems.

In a lecture, information relating to a particular concept is generally presented in a linear manner, and thus the student does not experience preliminary overall content impact. The student is required to simultaneously “understand” the concept as it’s being presented, in a manner consistent with the instructor’s logic, and jot down notes about it for future study. Many of today’s students are unable to do this effectively. An approach to this dilemma is to provide students with photocopied lecture outlines and notes. Indeed, this practice has become all pervasive in undergraduate pharmacy lectures lately. Presumably, this aids student understanding of the subject being covered. But it does not address the central problems with the lecture method which relate to student passivity, to diversity of individual styles with regard to learning, and to low perception of the required comprehension level.
Selection of an Alternative Method. Fortunately, there have emerged a variety of “active” strategies for classroom instruction, many of which have been summarized recently (4). It was believed that student understanding and valuing of drug biotransformation could be improved if the learning process was implemented in a stepwise manner. One of the most widely applied approaches to stepwise learning is the SQ3R (survey, question, read, review, recite) method (5,6), which was chosen to adapt to this application. The first three stages of this method, in which information was assimilated, would center on a reference document, rather than classroom lecture presentations.

Regarding the reference document, selection required evaluation of several comprehensive medicinal chemistry textbooks that contain chapters on drug metabolism. Three such textbooks (7-9) that appeared suitable for undergraduates were identified, and the first of these (7) was selected for use. Eventually it is anticipated that reference information as computer software presentations, derived from multiple sources and collected logically and accessible according to individual needs, will be available.

METHODS
In order to expedite the survey and questioning steps of the SQ3R process a series of study questions was provided to students in a Course Packet. These questions addressed, in consecutive order, fundamental points about drug metabolism narrated in the reference source. Class time was initially used to cover 5-10 of these study questions per class period. By this process, students were expected to assimilate, in their own chosen ways, factual information about drug metabolism.

Initial implementation of this approach resulted in an increased rate of coverage compared to traditional lecture delivery. However, nodding, yawning, passivity was still evident, as would probably be the case no matter what method of presentation was used in a large class such as this. Thus, during this process, the critical fourth stage, review of factual information, was begun.

For this application, the objective of the review process was to facilitate conceptualization of coverage and thus awareness of the comprehension level required for the examination. Thus, every third or fourth class period, students were assigned in class to write answers on notebook paper to a set of 3-5 review questions presented on an overhead transparency. These were based on selected study questions covered in the preceding periods. Each question was read out loud and input regarding jargon and meaning was requested. Students were told to work alone or in groups as they chose, referring to relevant study questions/answers worked out earlier in class. After about 30 minutes papers were collected. After class, student response patterns were noted. The next class period, each question was discussed with the focus on identifying and explaining any misunderstandings and amplifying key fundamentals.

In the final stage of the process, comprehension was measured using objective exam questions. Each exam question was derived from one or more of the study questions and/or review questions. As an example of the method, a selection of correlated study questions, review questions, and exam questions focussing on the structure and function of a drug metabolizing enzyme, cytochrome P-450, is contained in the Appendix.

During the last two weeks of classes, student assessment was obtained using an evaluation questionnaire, prepared and administered in a manner generally consistent with suggestions for obtaining valid student input (10). Students were asked: (i) What grade do you expect to receive in this course? (ii) What is your level of interest (scale: 5 = highest, 1 = lowest) in each of the four modules taught in this course? (iii) What instructional style do you prefer (lecture, discussion, or a combination of both)? Data on student interest in biotransformation (DM) was compared (Figure 1) with that in the two modules presented as lectures: Inorganic Medicinal Chemistry (ID) and Pharmaceutical Analysis (PA). Data on interest in discussion-based Drug Design/Drug Action instruction is not shown. The 1995 evaluation was obtained prior to the completion of the Drug Metabolism module.

RESULTS

Comparative Examination Performance. Over the past eleven years in which Introductory Medicinal Chemistry has been taught, student comprehension of drug metabolism has been determined using objective examinations. Performance as a function of instructional style over this time period is summarized in Table I. Recognizing that a score of not less than 70 is considered passing, these results amplify the problems associated with comprehension that were common when traditional classroom methods were in use. Thus, in 1991, about 50 percent of the class did not pass the module on drug biotransformation. Marked improvement in class averages has been seen since 1992, when discussion style coverage was first implemented.

Student Assessment of Discussion-Based Instruction. Besides drug metabolism, the Introductory Medicinal Chemistry course contained two other modules in which the lecture style of instruction was still used. Thus, it was feasible to ask students to indicate their interest in the subject matter covered in each of these modules, and with this kept in mind challenge them to indicate their interest, as well as their preference in instructional style, without regard to examination performance. Interest ratings are summarized in Figure 1. In 1994, about 80 percent of the students rated interest in drug metabolism above average (4 or 5), while the lecture based modules in inorganic drugs and pharmaceutical analysis received above average interest ratings from 66 percent and 53 percent of the students, respectively. Differences were even more pronounced among students expecting to receive grades of A in the course (“A” students). Interest ratings for biotransformation were not as favorable in 1995. During that year, course assessment had to be conducted prior to class coverage of some of the study questions and most of the review question portion of the Drug Metabolism module.

Results summarized in Figure 2 indicate a nearly equal preference for each instructional style, although “A” students as a group indicated that the discussion-based method was more suitable. Besides the above documented findings, a qualitative observation relating to student assessment was evident throughout recent offerings of Introductory Medicinal Chemistry: a major improvement in quality of student attitude prior to and subsequent to administration of midterm and final examinations was experienced.
Table I. Instructional style influence on exam performancea,b

<table>
<thead>
<tr>
<th>Years</th>
<th>Instructional style</th>
<th>Number of students</th>
<th>Average exam score</th>
<th>Percent (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>discussion</td>
<td>106</td>
<td>82.7 (11.3)</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>discussion</td>
<td>123</td>
<td>80.2 (12.6)</td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>discussion</td>
<td>121</td>
<td>76.1 (10.5)</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>discussion</td>
<td>119</td>
<td>83.9 (10.5)</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>lecture</td>
<td>100</td>
<td>69.9 (11.4)</td>
<td></td>
</tr>
<tr>
<td>1985–90c lecture</td>
<td>93–126</td>
<td></td>
<td>57.8–74.0 (9.8–11.8)</td>
<td></td>
</tr>
</tbody>
</table>

a Comprehension was determined using examinations, each of which consisted of 40-50 questions. Most questions were of the multiple choice type.
b Drug metabolism was covered over the last 10 class periods (hours) that the course met (1995), first 10 class periods (1992-4), last 15 class periods (1985-91).
c Average exam scores from these years are not always directly comparable to those from 1991-1995, because some of the examinations on drug metabolism given during these years contained questions addressing other instructional modules.

DISCUSSION

The results summarized in Table I, and Figures 1 and 2, indicate that discussion-based instruction in drug metabolism, as compared to traditional methods of instruction, has resulted not only in marked improvement in student performance, but also in a high perceived value of drug biotransformation knowledge. Little attempt has been made to examine other factors which may have contributed to observed improvements. Class size remained essentially constant over the years in which comparisons were made, and so presumably did the applicant pool size. Thus, an increase in overall student aptitude would not seem to be a contributing factor. Also, comparison of drug metabolism questions on examinations given from 1988-1995 suggested no radical change in degree of difficulty. Of importance in this regard, about 50 percent of the 1995 drug metabolism exam questions were taken verbatim from the 1990 drug metabolism exam, on which the class average was 65. Copies of the 1990 examination were not returned to the students.

Also noteworthy in Table I was the finding (see footnote b), that discussion-based coverage of biotransformation required only about two-thirds the amount of class time compared to when lecture-based coverage was used. This suggests that implementation of a discussion-based strategy would result in the opportunity to either increase the scope and/or the depth of coverage.

Although SQ3R has been used as a versatile educational method for many years, it seems to require combination with other techniques in order to produce optimal results(11-12). Accordingly, our successful application of SQ3R was due in large part to the regular assessment of in-class student written responses to review questions. This required students to review, in their own logical way and in a timely manner, the subject matter. It enabled us to identify jargon barriers, misunderstandings and comprehension gaps early. The flexibility of the process enabled us to conduct these review sessions during class periods which were best for the students [for example, not the hour before or after a big physiology or pharmaceutics midterm]. But most importantly, it empowered the instructor to judge the level of comprehension attained by the students, and to prepare examinations which would evaluate their knowledge in a realistic way.
they signify that a mixture of styles may be appropriate in a course, or even within a particular instructional module. The implication is that commitment to a single style of instruction throughout the course might have undesirable consequences. Second, successful conversion by a given instructor of a particular instructional module to a discussion-based style of instruction might depend on the nature of the subject matter covered in that module in relation to student capabilities and interests. For example, student performance over the last three years in the lecture-based modules in this course has been uniformly excellent, with exam averages ranging from 82.8 to 92.7. Conversion of these modules to discussion-based instruction would thus have to be approached with caution.

In the last several years, new ways for student-oriented large-class instruction in chemistry (13) and medicinal chemistry (14) have been described. Successful use of these approaches, the present one, or others that have been reported must be done in recognition that U.S. Pharmacy education, like U.S. science education, is of a diverse situational nature(15,16). Thus, assessment and modification of new methods, proximate to when they are being introduced, is critical for their success in the long run. Keeping these qualifications in mind, the discussion-based approach described here may be applicable to other chemical-structure-intensive medicinal chemistry course instructional modules.

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References
(4) Ellis, J.W., “How are we going to teach organic if the task force has its way?” ibid., 71, 399-403(1994).

APPENDIX. STUDY, REVIEW AND EXAMINATION QUESTIONS

Questions Used in Stepwise Learning About the Anatomy and Biochemistry of Cytochrome P-450.

OVERALL OBJECTIVE: to provide the student with the opportunity to maximize performance on examination items covering enzymatic oxidations of drugs.

OVERALL GOAL: to promote increased interest and understanding of oxidative drug metabolism.

Students use the reference document (textbook) to find and write answers to the following STUDY QUESTIONS (S1-S7)...

S1. Why is cytochrome P-450 a mixed function oxidase? Where does the name cytochrome P-450 come from?
S2. Why is CP-450 so nonspecific about what it accepts as substrates and how it oxidizes them?
S3. Why is allyl isopropylacetamide toxic to the liver?
S4. Show me the three phase I metabolites of benzene. In the phase I metabolite that contains two oxygen atoms, what are the sources of these oxygen atoms?
S5. Describe the NIH shift, which happens to p-deuterianisole (structure, below).
S6. Show how specific routes of hydroxylation of each of the three drugs shown below:

S7. How is aniline (C6H5-NH2) metabolized? Which of these metabolites causes blood toxicity? Describe this toxicity. What is the clinical significance of this?

...with contemporaneous review of assimilated factual information catalyzed by in class written response to corresponding REVIEW QUESTIONS (R1-R7)...

R1. What happens to molecular oxygen (O2) during the oxidation of a drug by cytochrome(s) P-450?
R2. Why are there so many isoenzymatic forms of cytochrome(s) P-450?

2The Study Questions in the APPENDIX were selected from a set of 56 drug metabolism study questions, prepared for use with the reference document (7)
R3. What change in the structure below would result in a chemical with NO liver toxicity? EXPLAIN.

\[ \text{Chemical Structure} \]

R4, R5. The substance below (p-deuteriobromobenzene) is metabolized by cytochromes P-450 to three metabolites, one of which does NOT contain D. One of the two metabolites which retain deuterium is “electrophilic”. Name or draw these metabolites.

\[ \text{Metabolite Structure} \]

R6. Which of the structures below (A-C) are metabolites of phenylbutazone? EXPLAIN.

\[ \text{Phenylbutazone Structure} \]

R7. Administration of which of the chemicals below would have the potential to cause methemoglobinemia? EXPLAIN.

\[ \text{Chemical Structure} \]

E2. CP-450 is a NONSPECIFIC enzyme with regard to substrates and routes of oxidation because of which of the following?
A. It produces highly reactive oxygen which reacts nonspecifically with substrates.
B. It is highly flexible and can thus bind drugs of varying sizes and shapes.
C. There are 20-25 isoenzymatic CP-450s, each with a slightly different substrate specificity.

E3. Allyl isopropyl acetamide (below) is metabolized by CP-450 to a toxic metabolite. This happens by oxidation of its group.

\[ \text{Allyl Isopropyl Acetamide} \]

A. CH a to C=O B. Allylic carbon C. n-Methyl

E4. Which of the following can be produced from the arene oxide which results from metabolism of the substance below by CP-450?
A. trans-1,2-dihydroxy-1,2-dihydrobenzene
B. 1,2-dihydroxybenzene
C. 1,4-dihydroxybenzene
D. trans-1,4-dihydroxy-1,4-dihydrobenzene

E5. The drug below is metabolized by CP-450 to p-hydroxy-methoxybenzene. 10% of the deuterium originally present in this drug is retained in the p-hydroxy-methoxybenzene. Therefore 90% of the p-hydroxy-methoxybenzene metabolite is produced via:
A. The NIH shift.
B. Direct insertion of an oxygen atom into a C-H bond.
C. Stepwise addition of oxygen atoms at m- and p- positions, followed by loss of water (H₂O).
D. Direct insertion of an oxygen atom into the C-D bond.

E6. Which of structures below (A-D) are metabolites resulting from oxidation of valproic acid?
E7. The substance below causes methemoglobinemia in animals. This is due to which of the following?

A. Its N-hydroxy metabolite converts ferrous hemoglobin to ferric hemoglobin.
B. This substance converts ferric hemoglobin to ferrous hemoglobin.
C. Its N-hydroxy metabolite forms a complex with hemoglobin and so prevents oxygen from binding.
D. Its p-hydroxy metabolite alkylates hemoglobin.