On-line, Individualized, and Interactive Pharmacokinetic Scenarios with Immediate Grading and Feedback and Potential for Use by Multiple Instructors

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On-line (web-based) pharmacokinetic modules were developed for 25 topics in basic and clinical pharmacokinetics. The modules consist of spreadsheet files, relational databases, and dynamic web. Instructors use a web browser to set up their class list, set/edit preferences (e.g., due date) for each module, and create on-line and e-mail reports of their students’ works. Students use a web browser to create an individualized assignment (scenarios without solutions) and unlimited practice problems (scenarios with solutions and graphs) and to submit their answers and receive immediate feedback. A test of the effect of innovation on students’ learning in a basic pharmacokinetics course indicated that the innovation caused a significant improvement in learning (~10 percent), compared with traditional use of assignments in a paper format. Additionally, students’ evaluations of the innovation were extremely positive. The innovation was also successfully used by instructors and students in two other sites. The innovation may be used as a tool in active learning strategies in pharmacokinetics courses, without a significant time burden for the instructor.

PROLOGUE

Recent advances in technology are significantly influencing the way pharmacy faculty teach courses such as pharmacokinetics. Currently, several stand-alone (not web-based) simulation programs are available(1-7) which allow users to change a kinetic parameter and/or dosage regimen data and observe the simulated plasma and/or urine concentration (or amount)-time data. Additionally, on-line (web-based) versions of the simulation programs have started to appear(8,9). These simulation programs are instrumental for understanding the concepts in kinetics. However, for the estimation of pharmacokinetic parameters and design of dosage regimens, instructors usually use the limited examples in the few available textbooks and/or develop their own set of problems and assignments which need to be graded manually. This is because, except for one spreadsheet-based program(10), there are no computer programs available to generate and grade pharmacokinetics assignments. The spreadsheet-based program(10) also has its own shortcomings including security problems, lag time for grading, requirement for a specific version of the spreadsheet program, access for off-campus students, and difficulty in transferability to other institutions (described in more detail in the next sections). Therefore, the major goal of this project was to develop a web-based pharmacokinetic program that would allow online generation and submission of individualized assignments with immediate feedback, which can be used by instructors of pharmacokinetics worldwide.

OUTCOMES COVERED BY THE INNOVATION

The desired outcomes of most basic pharmacokinetics course are:

1. prediction of the effects of alterations in the kinetic parameters and/or the dosage regimen data on the plasma and/or urine concentration-time data;
2. estimation of pharmacokinetic parameters from plasma and/or urine concentration-time data; and
3. design of dosage regimens based on the available kinetic parameters.

Although the program covers most concepts in basic kinetics (Outcome 1), its major focus is on the estimation of pharmacokinetic parameters (Outcome 2) and design of dosage regimens (Outcome 3).

DESCRIPTION OF THE TEACHING INNOVATION

General Description of the Course

Basic Pharmacokinetics is a required three-credit hour course which is offered to the fourth year students in the five-year BS program. Additionally, a modified version of the course will be taught starting next year in the entry-level PharmD program. The course is offered during the Fall semester with an enrollment of 107 students in the Fall of 1998. Learning is achieved in this course using a quasi problem-based, outcome-driven strategy(11) which combines some aspects of traditional instruction (large class size) with problem-based (limited lecturing) learning.

Previous Work and Its Limitations

Recently, the author developed(10) computer-assisted assignments and practice problems for twelve pharmacokinetic topics using the spreadsheet program Excel™. After installation of some macros on the user computer, these programs would allow generation of practice problems and assignments by random alterations of kinetic parameters and/or dosage regimen data within a preset range. A second set of macros on the
instructor’s computer would allow automatic grading of the submitted assignments in a batch. After four semesters of using these programs in large classes at Drake University College of Pharmacy, the following shortcomings were noticed:

1. **Security:** Because students are in possession of the spreadsheet files which contain both the scenarios/questions (unhidden) and answers (hidden), the security may be compromised.

2. **Excel® Requirement and Versions:** In order for students to use these files, they need to have access to computers which have a version of the Excel™ program compatible with the version used in the creation of the files.

3. **Ease of Use by Students:** Although installing the macros on the on-campus computers is not difficult, some students experience difficulty installing the macros on their own computers. Therefore, most students use the on-campus facility which results in some access problems. Additionally, electronic drop off of the assignments is available only on campus, making it inconvenient for off-campus students.

4. **Transferability to Other Institutions:** Several instructors of pharmacokinetics at the US and international Colleges of Pharmacy have indicated their interest in using these files. However, because of heavy protection of the files and macros (for security reasons), setting up the programs at other schools would be rather difficult.

5. **Grading Lag Time:** The assignments would be graded in a batch by the instructor using a separate macro, only after the due date. Therefore, students receive complete feedback after the due date, regardless of when they submit their assignments.

**Overview of the Current Innovation**

The innovation consists of several relational databases and spreadsheet files, located on a server. The server interacts with web browsers at the instructor and student sides as outlined in Figure 1.

**Instructor Side.** The innovation allows the author to assign a unique password and University ID to each instructor who is interested in using this system. Once this is done, the instructors may set up a class (Step I, Figure 1) by copying and pasting their students’ ID, set or edit preferences (Step II, Figure) for each assignment (e.g., due date, percent allowable error, number of times students are allowed to change their answers, and e-mail address where reports are sent after the due date). Each student has access to the page which displays their student information in a database, converts questions and graphs into HTML language, and sends them to the web browser for viewing (Step I, Figure 1) and printing (Step 2, Figure 1) by the student. These processes would take less than 4 seconds on the server side. For practice problems, both the questions and answers (including graphs) are sent back to the user. Once the student is ready to submit the answers to the assignment, he/she would access his/her record in the database and submit one answer at a time (Step 3, Figure 1). The student’s answer is checked against the correct answer in the database and a grade and the correct value are displayed in the web browser. This process avoids penalizing the student if subsequent answers are related to previous ones. Students may stop at any point during the submission of the answers and submit their answers to the remaining questions at another time until the due date set by the instructor. Each time they submit an answer, their grade will be updated.

**Detailed Description of the Innovation**

**Databases.** Using a commercial program, separate databases were designed for assignments and practice problems. Students were allowed to have access only to their own records, using a combination of their Student ID, University ID, and Assignment Name. Instructors had access to a separate database which contained one record for each assignment per instructor. All the databases were related to each other. Several scripts were written for handling the data and communication between the databases and the client (student or instructor) web browser and between the databases and the spreadsheet program.

**Spreadsheet Files.** A total of 25 files were developed each for a common scenario in pharmacokinetics. Each file would generate an unlimited number of assignments/practice problems containing the same general structure with different data. Additionally, depending on the topic, some questions would also be generated from several plausible scenarios. Each time a signal is received from the database, the spreadsheet program generates a new data set and exports it to the database. The spreadsheet files address the following topics:

- Slopes and Intercepts, First Order Kinetics, Zero-Order Kinetics, Single IV Bolus (Plasma), Single IV Bolus (Urine), PO Dosing, Oral Bioavailability, Constant IV Infusion, Multiple Dosing, Nonlinear Kinetics, Multicompartment Kinetics, Relationship Among Kinetic Parameters, Clearance Additivity, Hepatic Clearance, Renal Clearance, Therapeutic Drug Monitoring, Kinetics of Intermittent IV Infusion, Population Pharmacokinetics, Bayesian
Different formulations of drug kni known were administered to a group of volunteers at different occasions and the following data were reported:

<table>
<thead>
<tr>
<th></th>
<th>IV Solution</th>
<th>PO Solution</th>
<th>Tablet A</th>
<th>Tablet B</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE (mg)</td>
<td>10</td>
<td>20</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>AUC (ng.hr/L)</td>
<td>4.93</td>
<td>2.18</td>
<td>18.2</td>
<td>9.86</td>
</tr>
<tr>
<td>Cmax (ng/L)</td>
<td>6.853</td>
<td>2.83</td>
<td>1.27</td>
<td>0.678</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.67</td>
<td>0.67</td>
<td>3.6</td>
<td>2.9</td>
</tr>
</tbody>
</table>

1. Please determine the following bioavailability or bioequivalence parameters:
   1. The absolute bioavailability of the oral solution (F_oral)
   2. The absolute bioavailability of Tablet A (F_tabletA)
   3. The absolute bioavailability of Tablet B (F_tabletB)
   4. The relative bioavailability of Tablet A using PO solution as reference standard (FRelativeTo)
   5. The bioavailability of Tablet B relative to that of Tablet A (F_relativeB)
   6. The plasma profiles (AUC, Cmax, or Tmax) of the two tablet formulations are different because of (if all scenarios are possible)
      1. A difference in the rate of absorption
      2. A difference in the extent of absorption
      3. Both 1 and 2

II. A new formulation of Tablet A (A-2) is manufactured which has an F value twice as much (alternative: half) of the original value calculated in I with a rate of absorption identical to the original formulation:
   1. What is the expected AUC of the new formulation?
   2. What is the expected Cmax of the new formulation?
   3. What is the expected Tmax of the new formulation?

III. A third formulation of Tablet A (A-3) is manufactured with the same rate of absorption. However, the rate of absorption of the new formulation is faster (alternative: slower) than the original formulation. Compared with the original formulation:
   1. The AUC value of the new formulation is (circle one multiple choice) higher
   2. Lower
   3. The same
   2. The Cmax value of the new formulation is (circle one multiple choice) higher
   3. Lower
   3. The Tmax value of the new formulation is (circle one multiple choice) higher
   4. Lower

Estimation, Dosage Regimen Design-IV Bolus, Dosage Regimen Design-Intermittent Infusion, Dosage Regimen Modification, Route of Administration Conversion, Protein Binding, and Pharmacodynamics

Of the 25 files listed above, the first 15 were used in the basic pharmacokinetics course and the remaining 10 were designed for use in a PharmD course. As an example, an assignment for the topic of “Oral Bioavailability” is depicted in Figure 2.

Web Sites.

The innovation consists of two web sites, one for the students and the other for the instructors. The instructors’ site (Figure 3) consists of the following links: General Instructions, Set Up/Edit Your Class List, Create Preferences for Assignments, Edit Preferences, Generate an Online Report, Generate an E-Mail Report, and Go to the Students’ Page. The students’ site (Figure 4) consists of the following links: General Instructions, Generate an Assignment, Generate a Practice, and Submit/Retrieve Your Assignment.

Help Features.

In both the instructors’ site and students’ site, help is provided as general instructions and as hypertext links for all the necessary input or output parameters.

Major Advantages of the Innovation.

In addition to creation of unique assignments for each student and opportunity for unlimited practice problems, the current innovation has the following advantages over the previously reported spreadsheet-based files(10):

- **Ease of Use:** Generation and submission of assignments occur on-line using a few links, and all the processing is accomplished on the server. Therefore, there is no need for any specialized software or macros on the user side as long as an internet connection and a web browser are available to the user.
- **Access:** Students can access the server from both on-campus and off-campus sites, even if they are out of town.
- **Security:** Because all the information is saved on the server (rather than on the student’s computer), there is more control over the data. Additionally, there is no need for heavy protection of spreadsheet files because they are not available to students.
- **Immediate Feedback for Individual Questions:** One of the problems that most pharmacokinetics instructors encounter is the issue of partial credit for multipart problems related to each other. Because students receive the correct answer and their grade for each question before they proceed to the next question (Fig. 5), this problem is avoided in the on-line modules. Additionally, it is more likely that students learn from their mistakes and do not make similar mistakes in the subsequent sections of the assignment.
- **No Time Commitment by the Instructor for Grading:** On-line grading will alleviate the problem that all pharmacokinetics instructors are faced with when administering homework assignments.
- **Potential for Use by Instructors and Students at Other Institutions:** Once a record is set up for a University, the modules may be used by that University instructor and students without any need for any local set up procedure. Already, the innovation has been successfully used by
instructors and students at the University of Alberta Faculty of Pharmacy (Edmonton, Canada) and Western University of Health Sciences College of Pharmacy (Pomona, CA).

**Major Disadvantage.** Contrary to stand-alone programs, an on-line program like this innovation requires access to the internet. This also means that when the internet at the server side or the client side is down, the program cannot be used. However, considering the easy availability of internet access on university campuses and rapid expansion of internet access via other sources (e.g., public libraries) and at home, access does not appear to be a limiting factor. Further, internet speed and reliability are improving at a very rapid rate.

**Other Innovations Used in the Course**

In addition to the development and application of the on-line assignments/practice problems described above, the following tools were also developed and incorporated into the course.

**On-line Pharmacokinetic Simulations.** The same principles used for the development of on-line assignments/practice problems were employed to develop on-line modules that students can use to test “what-if” scenarios which would help them in understanding the concepts. Currently, simulation modules have been developed for the following topics: Pharmacokinetic Concepts (IV), Pharmacokinetic Concepts (PO), Bioavailability and Bioequivalence, IV Infusion, Multiple Dosing, Nonlinear Kinetics, and Hepatic Clearance. These modules would allow students to enter pharmacokinetic parameters and dosage regimen data for two cases and observe the effects of changes in the kinetic parameters and or dosage regimen data on the other kinetic parameters and the plasma concentration-time courses. Additionally, these modules were used for in-class demonstration of concepts. Similar to the assignment modules, the simulation modules have an extensive on-line help feature along with specific objectives and examples of data. However, it should be noted that contrary to the on-line assignments/practice problems which are unique, there are at least two other reported on-line simulation modules.

**On-line Gradebook.** The basic pharmacokinetics course taught in the Fall of 1998 consisted of 5 exams, 15 assignments, and 25 quizzes. One of the comments of students from previous classes has been that they would like to have up to date information about their grades in the class frequently during the semester. For the Fall of 1998, a gradebook was developed, using a database program, and published over internet. Students would access the search page and after entering their ID would access their up to date grades at any time and from anywhere. Both summary (Overall Assignments, Overall, Quizzes, Overall Exams, and Tentative Class Grade) and detailed (individual assignments, quizzes, and exams) reports are provided. Students have found this feature to be very beneficial (Please see the Evaluative Data Section).

**Integrated Delivery of the Course Materials.** All of the above materials along with electronic discussion forums, reading handouts, objectives and outcomes for each topic, and example practice problems and their solutions are integrated into one web site using the “Web Course in a Box” software (Madduck Technologies, Richmond, VA). A version of this software is available to academic institutions free of charge (http://www.madduck.com/+).

**EVIDENCE OF STUDENT LEARNING**

Traditionally, students in pharmacokinetics courses are provided with take home assignments which would be the same for all students. After the due date, the instructor and/or teaching assistants would grade the assignments and return them to students. This process results in a delay between the time that students submit their assignment and the time they receive feedback; in most cases, the graded assignments are returned at a time when students are concentrating on the next topics. Additionally, some of the questions may follow similar concepts. Therefore, students may lose points in multiple places.
related to the same concept. Lastly, although practice problems may be worked out during the class time, the students normally do not have access to unlimited practice problems. Therefore, aside from convenience to both instructors and students, the main differences between the effects of traditional assignments (paper format) and the innovation (on-line format) on learning are due to provision of immediate feedback for individual questions and availability of unlimited practice problems using the on-line format.

In order to test the effect of innovation (unlimited practice problems and immediate feedback on individual questions) on learning process, the P-4 students enrolled in Basic Pharmacokinetics during the Fall of 1998 were divided randomly into two groups: Group 1 (n = 54) and Group 2 (n = 53). While Group 1 received one of the assignments (Clearance Additivity, Assignment 1) using the traditional paper format, Group 2 used the innovation. The paper assignments were generated by the instructor and made available to students. The students using paper format were not allowed to use the innovation for generation of practice problems or submission of their answers. Instead, they were instructed to submit their answers on paper. All students (both groups) were provided with one practice problem and its solution during the class time. For the next assignment (Hepatic Clearance, Assignment 2), the groups were switched: Group 1 used the innovation, while Group 2 was provided with the paper assignment. The grades that students received in these assignments are listed in Table I.

As demonstrated in Table I, the students who used the innovation (on-line format) scored approximately 10 percent higher (P = 0.0024, repeated measure ANOVA) than those who used the traditional paper format, regardless of the groups or the assignments; there was no difference between the groups (P = 0.3865) or the difficulty of the assignments (P = 0.6181). Incidentally, the score of the students who used the on-line format was the same for both assignments (Table I). Another notable finding is that the variability in the grades for the paper format (32 and 25 percent for Assignment 1 and Assignment 2, respectively) was 2.5-3 fold of that for the on-line format (~10 percent). Further, the number of students receiving a grade of <80 percent was substantially greater for the paper format, suggesting a more substantial effect of innovation on learning of students with lower abilities. The latter is most likely due to provision of multiple opportunities for practice using the innovation.

### EVALUATIVE DATA
At the end of the Fall semester, a survey was distributed among the students, and the students' perception of the innovation was evaluated in an anonymous manner. The survey was based on quantitative questions using the rating scale of Strongly Agree (1), Agree (2), Neutral (3), Disagree (4), and Strongly Disagree (5).

The results are presented in Table II for 19 questions. Generally, the response of students to the on-line assignment/practice modules was extremely positive. Most students agreed or strongly agreed that the use of innovation was easy (Questions 2-5) and that the innovation facilitated learning (Questions 1, 7, 8, 10, and 12). Of particular note is the fact that >85 percent of the students strongly agreed that they frequently generated and used practice problems before working on the assignments (Question 6) and that the practice problems were helpful for understanding and completing the assignments (Question 7). However, the responses of students to the simulation modules (Questions 14-17) were not as positive as those for the assignment/practice modules. This may be due to the fact that the use of simulation modules was voluntary (no grade was assigned), as opposed to the mandatory use of assignments. Indeed, as the response to question 15 (Table II) indicates, students generally did not use simulation modules outside the class (only 16 percent of students (strongly) agreed with the statement for this question).

Students responded (Table II) most positively to receiving immediate feedback feature and convenience of the modules (Question 9) and having access to their grades using the grade book (Question 18). Overall, more than 95 percent of the class (strongly) agreed that the use of computers in this course is worthwhile and should be continued (Question 19).

### PERSONAL REFLECTIONS AND FUTURE DIRECTIONS
The author's experience in teaching pharmacokinetics to large classes (>100 students) has made him realize that without practice and active involvement of students, significant and long-term learning seldom occurs. Additionally, students learn better if they are given feedback in a timely manner. Unfortunately, given the personnel resources available at most Colleges of Pharmacy (especially those without graduate programs and teaching assistants), provision of multiple opportunities for practice and timely feedback is difficult, if not impossible. This is because pharmacokinetics instructors have traditionally designed and used pharmacokinetic scenarios as take home assignments for their students. However, because of the significant time commitment for design and grading of these assignments, relatively limited practice opportunities have been afforded to students. Therefore, the author has been actively searching for alternative methods to allow him (and possibly others) to provide students with unlimited access to practice problems and assignments with opportunity to receive immediate feedback, without a major time commitment on the part of the instructor.

The author's initial efforts led to the development of 12 spreadsheets using the Excel program(10). After installation of several macros on the user computer, these files would allow generation of assignments (for grading) and multiple practice problems (for practice). This was a major step forward, considering that no other comparable program was available. However these files required installation of specialized programs and macros on the user computer, posed security problems, and required use of a local area network for submission of assignments (available only on-campus). Additionally, there was a lag time between the submission of the assignments and grading (for complete description of limitations, please see Previous Work and Its Limitations section). After developing these files, several colleagues from other institutions indicated an interest in using them. However, because installation and use of these files required significant knowledge of the instructor about details of the system (such as protecting and unprotected files during grading) and specialized software, this did not seem to be realistic. Considering all of these issues, the logical solution was to develop on-line (web based) modules.

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Table I. Effect of innovation (on-line format) on the students’ grades in two assignments

<table>
<thead>
<tr>
<th>Groups</th>
<th>Assignment 1</th>
<th>Assignment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83.7 ± 26.4 (Paper Format)</td>
<td>93.6 ± 10.6 (On-line Format)</td>
</tr>
<tr>
<td>2</td>
<td>93.6 ± 9.2 (On-line Format)</td>
<td>84.4 ± 21.0 (Paper Format)</td>
</tr>
</tbody>
</table>

P = 0.0024 for the difference between the paper and on-line formats. 
N = 54 for Group 1 and 53 for Group 2
which would devoid of the problems associated with the spreadsheet files and would allow other instructors and students to use them. This was achieved by simultaneous use of three major components: relational databases, spreadsheet files, and dynamic web. The resultant innovation was successfully used in assisting learning during the Fall of 1998. Overall, a total of 25 modules were developed which cover most topics discussed in basic pharmacokinetics courses and some topics in more advanced clinical pharmacokinetics courses.

The students' response to the innovation was so positive that when the author decided to divide the class into two groups to test the effects of innovation on learning, the students expressed disappointment in that they could not use the on-line modules for one assignment. A number of students stated that the opportunity to generate and use unlimited practice problems and to receive immediate feedback on assignments was invaluable to them. This sentiment is also reflected in the final evaluation of the innovation by the students (Table II).

Despite overwhelming success of the assignment/practice problem modules, the implementation of the simulation modules was not very successful (Table II). This may be due to the fact that students did not see any incentive to use these modules. Perhaps, the use of simulations should be made mandatory in the future and/or a grade should be assigned to it.

Another modification planned for the future is inclusion of more concept (multiple-choice) questions into the assignment/practice modules. Currently, a majority of the questions are related to calculation of kinetic parameters and/or design of dosage regimens; the concepts are mostly covered in the simulation modules. Inclusion of more concepts in the assignment/practice modules would compensate for a less than optimal attention to the simulation modules.

An additional modification based on the suggestion of some students is the provision of a more in-depth feedback than simply providing the correct answers. Therefore, equations, concepts, and the methods of arriving at a particular answer could be incorporated in the future versions of the modules.

Lastly, the modules have been successfully tested, although on a limited scale, only in two other universities. The author plans to make the modules available to other interested colleges of pharmacy in the next year to examine its robustness when several universities use it simultaneously.

Acknowledgment. The author would like to thank Joseph D. Scavo for helpful discussions and suggestions regarding the use of different databases and also for administration of the server. The voluntary participation of the students in evaluation of this innovation is also acknowledged.

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