

KEY WORDS

Pharmacokinetics, modeler, hands-on, safety, practical class, clinical training.

ABSTRACT

After swallowing or injecting a drug, the magnitude and duration of drug effects, therapeutic and unwanted, are determined by how rapidly the drug is absorbed, distributed to organs, and cleared from the body. The study of the mathematical principles underlying these processes is called pharmacokinetics. Safety and ethical concerns now preclude use of animals and human subjects in labs designed to teach pharmacokinetics, so students must rely on didactic lectures to convey the essentials - and they struggle badly. To address this, we have designed a unique apparatus which mimics handling of drugs by the human body, allowing students hands-on experience administering drugs and analysing pharmacokinetic behaviour in a risk-free setting. We propose to construct several apparatus and use these to model clinical scenarios in an undergraduate laboratory course. The effectiveness in enhancing comprehension in a student cohort previously taught and examined in a solely didactic setting will be assessed.

PROJECT DESCRIPTION

Background to the problem

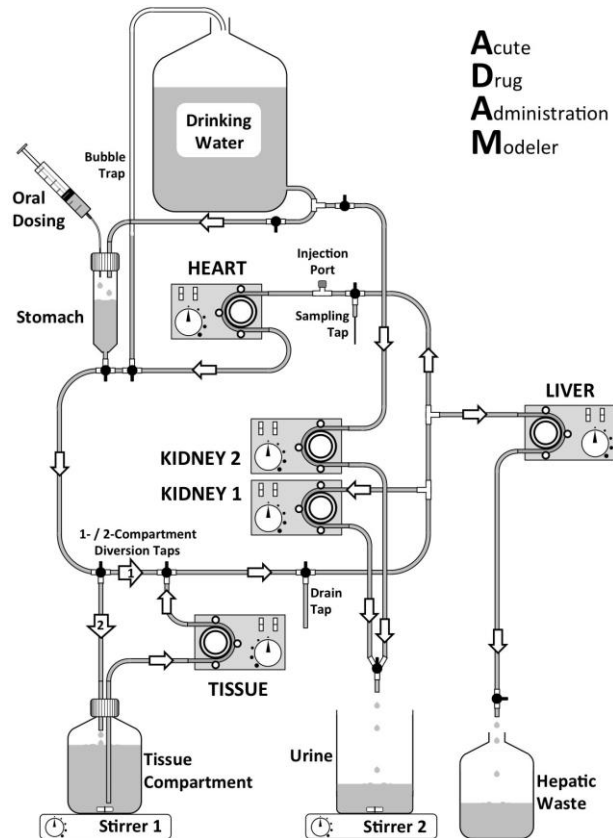
Following oral administration of a drug to a patient, the onset, magnitude and duration of drug effect are determined, in part, by the dose administered, and by several pharmacokinetic (PK) parameters. These parameters include the rates and extents to which the drug is absorbed from the GI tract into the systemic circulation and to which it distributes between blood and tissues, as well as the rate at which the drug is cleared by renal elimination and/or hepatic metabolism. Plotting drug concentrations in plasma (or urine) samples drawn at numerous time points following administration generates a plasma (or urine) concentration-time profile for the drug, with the shape of the curve for any given drug determined by a patient's PK parameters ⁽¹⁾.

Mathematical analysis of concentration-time data in an individual provides critical information relating to drug absorption, distribution and elimination, ultimately allowing the clinician or clinical pharmacist to select an appropriate acute or chronic dosing regimen that will achieve the desired therapeutic effect while avoiding unwanted side-effects ^(1,2). Indeed, recommended dosing regimens are based upon PK information obtained from larger numbers of volunteers in clinical trials. An appreciation of the mathematics underlying these analyses thus allows clinical personnel to understand how PK parameters determine therapeutic response, and how this response might change if the dosing regimen is altered, or if the drug is instead administered to a patient with, for example, renal insufficiency, hepatic impairment or enzyme induction.

In years past, students of the clinical sciences became proficient in pharmacokinetic analyses through a combination of didactic lectures and hands-on experimental approaches using small mammals and even human (student) volunteers ⁽³⁾. However, ethical and legal considerations now preclude these hands-on experiences, and students are expected to master the approaches simply through reading lecture notes and attempting theoretical calculations. In the Department of Pharmacology, I teach PK to 2nd year B.Sc. students as part of a single term lecture course. There is no doubt that our students find this topic more challenging, and struggle to a greater degree, than with any other area covered in our program ⁽⁴⁻⁶⁾. In Pharmacy, Medicine, and Nursing courses, PK is covered rather briefly, at a basic level, in early introductory lectures. Although recent studies have confirmed that active learning techniques significantly enhance students' understanding of PK concepts ⁽⁴⁾, no hands-on opportunities are offered to any undergraduates at the U of A, or indeed at most universities. The result of this is that few students can relate theory to clinical application, critical concepts are not reinforced, and a depth of understanding of PK is not developed in the vast majority of students.

We have designed and assembled a prototype apparatus that allows clinical science trainees to administer a drug to a "patient", either orally or intravenously, and collect samples of plasma or urine over a period of time. Drug concentrations are then determined in each sample and plotted appropriately, prior to mathematical analyses of the data. Patient PK parameters can be adjusted to

reflect altered physiology or pathophysiological changes. The apparatus closely simulates drug handling by the human body and offers a "clinical" experience, while avoiding ethical and safety issues associated with use of human volunteers or animals. We propose to complete development and testing of the prototype, construct several sets of the apparatus, prepare a laboratory manual detailing several possible clinical scenarios to be examined, and introduce the apparatus in an undergraduate practical class. We will assess the effects upon students' understanding of PK principles; we expect to observe a clear benefit, and we will then make the technology available to other users at the U of A, and to a wider audience. In this regard, we have signed a commercialisation agreement with TEC Edmonton, and an initial patent assessment is ongoing.



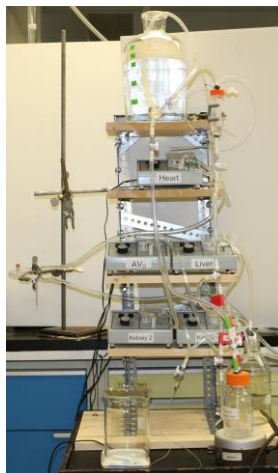
Apparatus details

The apparatus (below) is comprised of five peristaltic pumps plumbed together with Tygon tubing, as illustrated. The HEART pump circulates water (blood) through the system. Hepatic clearance is set through the LIVER pump flow rate. Renal clearance is set through the KIDNEY 1 pump flow rate, with total urine output kept constant through balancing urine volume with the KIDNEY 2 pump. Lost volume is replenished in real time by gravity feed from the *Drinking Water* reservoir into an airtight *Stomach*. The volume of distribution is modified by changing the volume in the *Tissue Compartment* bottle, while the rate and extent of distribution (and inter-compartment transfer rate constants) are set through the TISSUE pump flow rate. The *Tissue Compartment* loop can be isolated with *Conversion Taps* to convert drug behaviour from 2-compartment to 1-compartment. Oral bioavailability less than 100% is achieved by providing students with a stock drug solution for oral administration at a than that stated.

concentration lower

The drug administered fluorescent drug, such injected IV through an into the *Stomach*. Rate the initial volume of allows regular urinary drug levels can the *Urine* waste flask. spectrophotometrically used to quantify

A photograph of the apparatus. The front



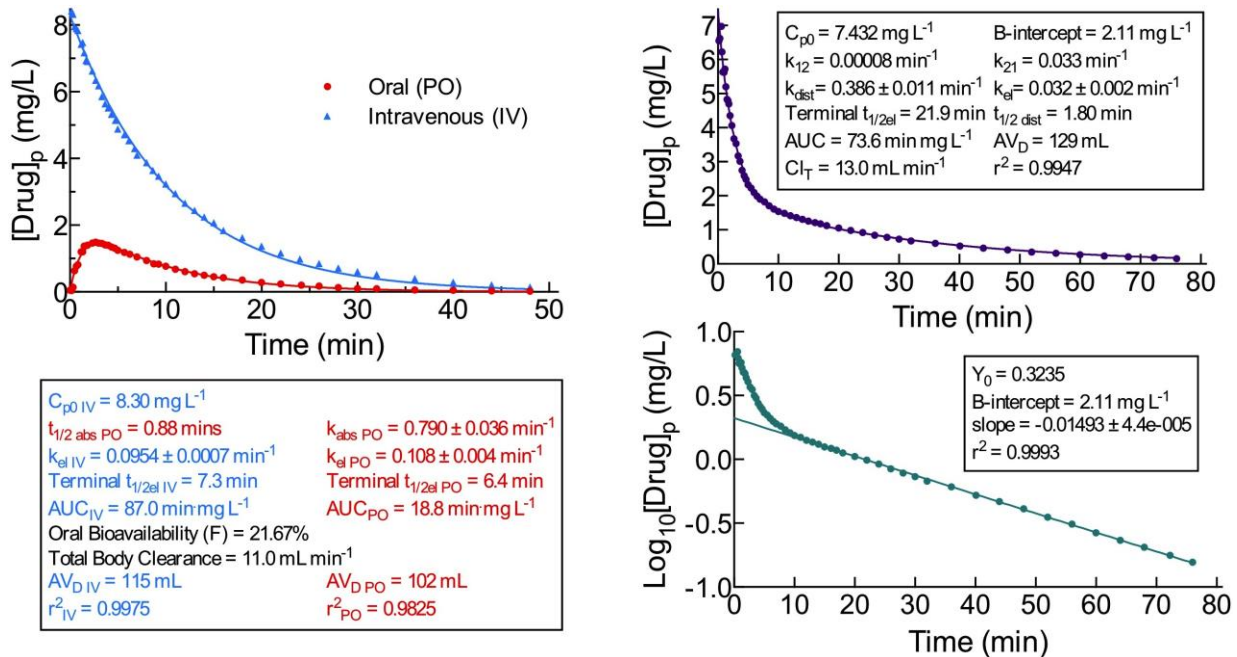
is methylene blue (although any coloured or as quinine, could be used). The drug can be *Injection Port*, or administered by *Oral Dosing* of absorption is regulated in part through altering water in the *Stomach* container. A *Sampling Tap* collection of small aliquants of blood, while be determined from samples taken regularly from Drug concentrations are determined in a 96-well platereader; absorbance at 664 nm is methylene blue.

prototype (right) shows the rear view of the view visible to the students shows a full-size

cartoon outline of a patient mounted on a foam board, with an outstretched arm revealing IV injection and sampling ports, an oral feeding tube for PO administration, and a catheter for collecting urine.

Example data

The figures on the following page show example data from a one-compartment experiment (left panel) in which drug was administered orally and IV, and from a two-compartment experiment (right panel) following IV administration, plotted on linear (top) or \log_{10} (bottom) y-axes to reveal a classical "hockey stick" semilog plot confirming two-compartment kinetics. Data panels highlight some of the PK parameters that can be calculated.



Laboratory manual and practical class outline

The flexibility of the system allows several practical classes to be designed to study a variety of PK parameters. We will create a user manual that outlines eight unique practical classes that can be taught, ranging from basic concepts to complex kinetic analyses. Initially, we will design two experiments to run in consecutive weeks in our PMCOL337 3rd year laboratory class; these classes are currently scheduled for March, 2015. We plan to have three sets of apparatus in place for a class of 18 students. Identical doses will initially be administered by each group, but the three apparatus will be set up differently to model inter-individual variability in PK behaviour.

Week 1. Each student group will administer the same dose of drug, both IV and orally, and will collect plasma and urine samples for one hour. Drug concentrations will be plotted appropriately, and PK parameters will be determined: these will include elimination half-life and rate constant, initial and terminal volumes of distribution, total body clearance, hepatic and renal clearance, oral bioavailability, and confirmation of the number of compartments. Groups will compare results and will answer questions regarding variability.

Week 2. Before the class, students will calculate the IV and oral dosing rates required to achieve a steady state concentration that lies within a given therapeutic window, based on the PK parameters calculated in week 1. They will then administer drug chronically following their proposed dosing

regimen, by IV infusion (one group) or repeated IV injections (2 groups) and then by repeated oral administration (all groups) and will sample plasma regularly and plot concentration-time data to confirm that their calculations were correct.

Summative and formative assessment

Students will complete work booklets for each practical class, in which they will plot their data, record calculations and answer clinical questions. These booklets will be marked, and marks will contribute to their overall score for the PMCOL337 course. In addition, as part of this TLEF proposal, we will assess the perceived and measurable enhancement in understanding of PK concepts in students who have already completed a pharmacology course (PMCOL201) in which PK concepts were taught. This assessment may take the form of before- and after- online quizzes, and self-assessment questionnaires, and possibly comparisons with exam performances of the same students in PMCOL201 (we await confirmation of whether or not ethics approval will be required). We have a meeting scheduled for January 15th with Dr. Ken Cor of CTL, the Director of Assessment in the Faculty of Pharmacy, to discuss the most appropriate assessment strategies, as well as potential future use of the apparatus in the Pharmacy undergraduate program.

Alignment with TLEF goals and *Dare to Discover*

Innovation The apparatus we have designed is unique; a TEC Edmonton-initiated search has revealed no other similar system offering students the life-like PK experience that we propose. Patent lawyers from TEC Edmonton will meet with us in February to discuss the filing of a US patent. The apparatus is easy to construct and is relatively inexpensive, and so will be within the reach of any Department teaching PK concepts to clinical and life science students. ***Collaboration*** Initial development has been carried out in my laboratory. Following successful proof-of-concept in a lab class setting, we will collaborate with the Faculty of Pharmacy initially with a view to introducing the approach to the PHARM curriculum. ***Evaluation*** My graduate student, Ines Zuna, has been attending the GTL program to develop her teaching and assessment skills, and has spearheaded our efforts in seeking feedback from the CTL with regard to the most appropriate assessment strategies. An ability to demonstrate enhanced understanding of PK principles as a result of exposure of students to this novel approach is critical if we are to "sell" this idea beyond our own program. ***Sustainability*** The apparatus and associated manuals will be available for many years for use at the U of A, with nothing more than occasional preventative maintenance (replacement of tubing and plastic components) required. ***Impact on students*** This approach offers our students a unique, memorable and reinforcing experience unavailable anywhere else. We believe the apparatus will grab their attention; they can "play Doctor", experimenting with dosing regimens without risk to patients or animals. The apparatus is constructed on a mobile cart, and it will also be possible to take the cart to a lecture theatre and perform live demonstrations to large lecture classes. Understanding how the system models PK parameters will also assist students in understanding what these parameters actually mean; the value of the system in this regard should not be underestimated. ***Dissemination*** We will soon begin preparing a manuscript for submission to the *British Journal of Clinical Pharmacology*, who have expressed an interest in this endeavour. We will prepare a podcast demonstrating the apparatus in action and will showcase the apparatus at meetings of the Canadian Society of Pharmacology & Therapeutics. Further dissemination plans must await the outcome of patent discussions. ***Dare to Discover*** Our proposal will offer students a dynamic, discovery-based learning environment where they will experience an exceptional and unique learning opportunity, increased subject engagement facilitating development of

professionals more conversant in PK principles in fields where a lack of understanding can have devastating consequences for patients.

Proposed activities supported by TLEF funding

The requested funding would partially (20%, 2 years) cover a graduate student's stipend to complete testing of the prototype apparatus, assist in preparation of a protocols manual, research and develop the assessment procedures and modify experimental and assessment procedures and protocols based on feedback. Funding is also requested to purchase materials to construct FOUR further units, to provide five in total, and to provide open access to our planned publication.

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