

Pre-ingestion Pharmacokinetics: Neglected Variables

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Pharmacokinetic principles have been valuable guides to therapy for years, and are well-described in standard textbooks.¹ A limitation common to all of these principles, however, is that they begin their considerations at the time of administration of a drug. The purpose of this paper is to introduce the concept of a pre-ingestion pharmacokinetics, which we believe, in its net effect, is far more powerful than post-ingestion pharmacokinetics. We acknowledge that most of the principles we are advancing have been formulated under other rubrics, such as “patient adherence.” We believe that it may be useful to consider these variables as a kind of pharmacokinetics amenable to mechanisms established previously in post-ingestion pharmacokinetics and forming a bridge between pharmacokinetics and the science of human behavior.

The Intention to Prescribe

The earliest movement of a drug is from unconscious drug-file engrams in a physician’s brain to a conscious intention to use a drug. Many carrier proteins have been identified that may serve to move the drug from this step, and they have been divided into two classes. There are the pharmaceutical-company proteins and the residency-associated proteins. It will be readily observed that there is binding-site competition between the pharmaceutical companies’ blandishments and the engrams planted 18 years ago during residency of drugs now off patent. Pharmaceutical company proteins have evolved multiple binding sites to increase the valence of their carrier proteins such as: comely representatives, physician enlistment as bogus paid “consultant,” free meals, and recruitment by ads to the public to be lay representatives clamoring for the latest arthritis drug.

Drugs in the physician engram have side chains with an affinity for pharmaceutical doodads. Penlights, pregnancy calculators, and refrigerator magnets are the most common moieties at these locations. All share a proprietary drug name emblazoned on the surface.

The Initial Physical Event

Once a drug has been selected by the physician operating under these kinds of influences, the first physical manifestation of the drug occurs when it is scribbled on a small rectangular paper. This movement from neural concept to physical representation establishes the baseline time, T_0 , by which other kinetics are measured. The drug at this point is known as the “inscribed drug.”

There are numerous transcription errors at this step. Physicians are equipped with almost uniquely sloppy transcription machinery. Some of the resultant errors are corrected by a feedback mechanism between the prescribing physician and the pharmacist—called “phoning”—but this correction requires inordinate amounts of energy compared to that allotted by the larger system to the transaction. The available energy limit is set by a device known as

the AWP, which operates on the pharmacy organ. AWP is similar to ATP and ADP in that it is the ultimate energy source for the pharmacy organ.

In the interests of larger organism efficiency, the AWP allotment requires the pharmacy organ to operate at a bare margin of survival, a limitation that has only slightly been overcome by pooled pharmacy purchasing. Each feedback correction required by the pharmacist because of poor physician transcription puts the energy balance into the negative column for the pharmacy, a source of some inflammation. The thrust of evolutionary development at present is toward extinction of pharmacy organs that are not part of larger systems. Several decades ago, pharmacy organs added energy to the system through the sale of greeting cards, hair brushes, candies, and the *National Enquirer*. The increase in energy was temporary, as the AWP merely declined in proportion. More recently the pharmacy organs added energy by including herbal remedies, but the increases have been quite modest. These maneuvers can be collectively described by the general formula: $E = AWP(X)$, where E = the financial energy available to the pharmacy, AWP = the average wholesale price, and X = the economic survival maneuver of the evolving pharmacy.

Pathway from Medical Premises to Pharmacy Organ

The inscribed drug moves from the physician’s hand to the purse or pocket of the patient, and exits the medical premises, ostensibly destined for the pharmacy organ. At this point, 5.2 - 22% of the inscribed drugs disappear.^{2,3} Various explanations, mostly hinging on quantum theories by which pocketed inscribed drugs oscillate between existence and nonexistence, have been proposed for this disappearance. Some inscribed drugs have been located in area trash bins and others may become part of roadside litter, but careful prospective studies addressing this matter are rare. Some inscribed drugs reappear in purses and pockets up to a year later, establishing outside estimates of the periodicity of the oscillation for the quantum theorists. Another reappearance mechanism exists when unscrupulous people sort through the trash of pharmacies to pull out prescriptions. This motion is described in Figure 1 by the K_i constant, where K_i represents potential illegal activity. It will be noted that K_i appears in more than one reaction.

For the inscribed drugs that do not oscillate into nonexistence, there is a movement of variable velocity toward a pharmacy, sometimes occurring in minutes though it may be delayed for weeks. Drugs that alter the patient’s mental state toward relaxation, “buzz,” or “mellow” tend to move most rapidly to the pharmacy. Those which alter only some invisible biochemical quality, such as cholesterol or bone calcium density, tend to be transported more slowly. Velocity of movement is inversely related to cost ($V_{\text{pharmacy}} = \text{drug dose/cost}$).

Studies indicating that ingested drugs are efficacious err on the side of effectiveness owing to these features. Pharmaceutical studies all provide the drug at no cost to the experimental patient, thus removing a significant barrier that exists in “real life.” Further,

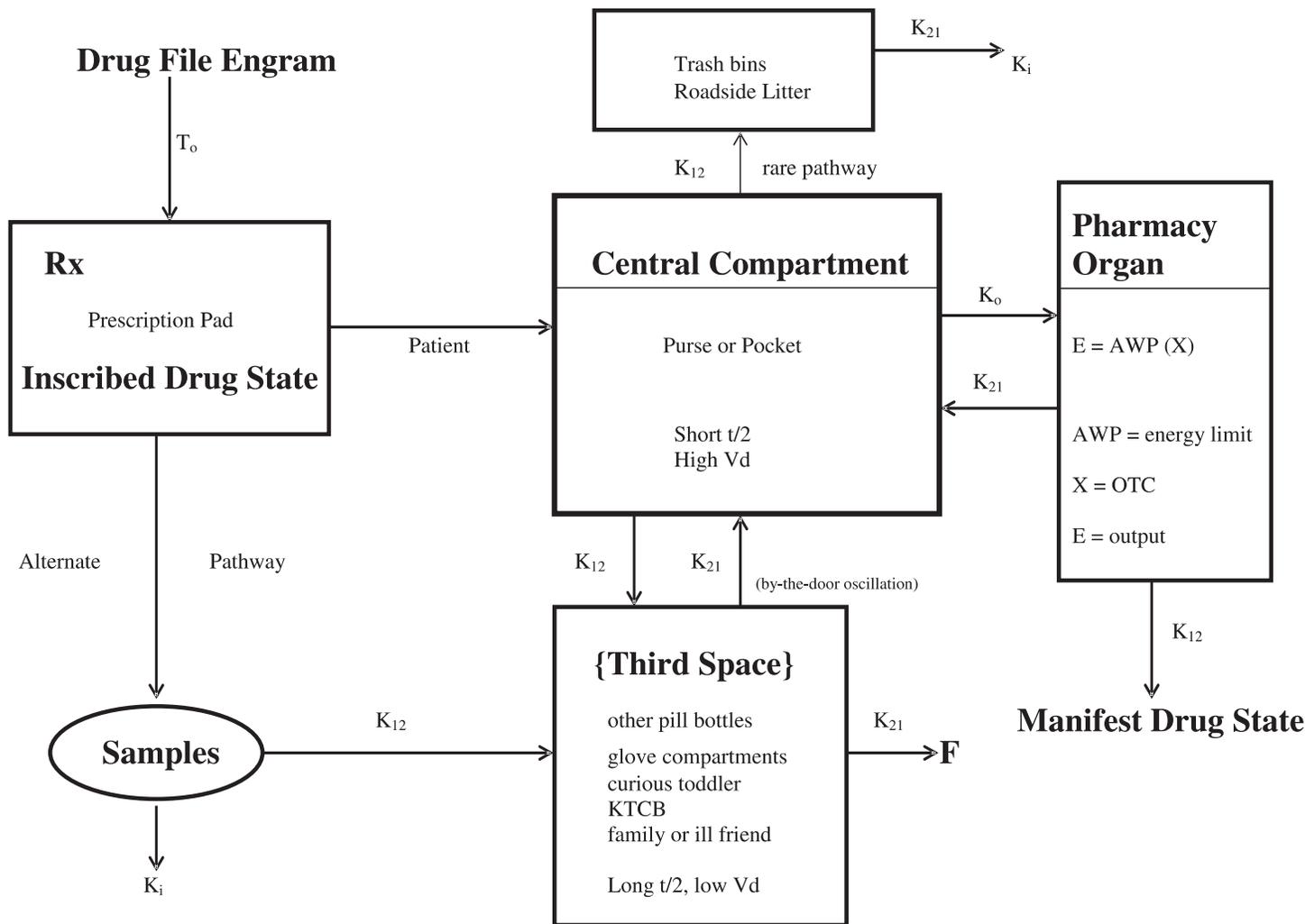


Figure 1. Pre-ingestion Pharmacokinetic Modeling

K_0 = rate of purchase, K_{12} = compartment uptake constant, K_{21} = compartment release constant, K_i = potential illegal activity constant, F = Bioavailability, T_0 = time, $t/2$ = half-life, V_d = distance volume, KTCB = kitchen table/bathroom cabinet space

recent studies have been incorporating a pre-selection phase with various measures of pretended purpose taking place. An unstated effect of this phase is to eliminate those patients who won't follow through in the experiment because of lack of commitment, lack of transportation, or when they realize that the drug won't mix with marijuana. "Real life" prescription of the drug, of course, does not eliminate these variables, and the inscribed drug hits the trash bin or molders in a wallet unfilled, producing a decrease in the efficacy.

Drug Reaches Manifest Chemical State

It is in the pharmacy organ that the drug moves from its "inscribed drug" state to its manifest chemical state. In this state it is potentially bioavailable, but there is one more elimination pathway for it even while it is still in its inscribed state—the financial elimination route. This elimination takes place by means of the selective permeability function of the pharmacy counter information window. When the patient discovers that the cost of the entire prescription is \$102.50, he asks the pharmacist how many tablets \$10.00 will purchase, and seeks that number. This shift, naturally, can be managed later in the elimination pathway by taking only one tablet weekly instead of daily, by random skips based upon one's guess as to the blood pressure of the moment, or by omission of approximately 90% of the doses.

Intermediate Steps in Transport of Actual Drug

The earliest compartment of drugs in their manifest chemical state is the purse (in females) or the pocket (in males). Though uncommon, there are various drug-drug interactions that take place either in the purse/pocket or during transfer in and out of this compartment. Inattentive manual withdrawal of the drug sometimes results in extraction of the wrong drug. This possibility is increased among patients with poor vision, impaired alertness, or in conditions of low light. In rare instances, even non-drug substances are withdrawn and ingested, usually with minimal harm, as in the case of Tic-Tacs, but occasionally the substance can be quite noxious as in the case of cat fur balls being transported to the veterinarian for analysis.

In the cause of compactness of transport, the patient often transfers drugs from their original carriers into a third space, often a single carrier, the label of which may reflect none of the actual contents. Despite elaborately evolved shape-and-color coding, the drugs are frequently ingested inappropriately, attenuating if not erasing their benefit. Evolution of brightly colored stickers coating the exterior of the container also has had limited effect upon this error.

From the purse/pocket compartment some drugs move to a third space in the form of the glove box/car seat. Drugs susceptible to light or heat degradation, especially the latter, deteriorate

proportionate to the heat and light. Chronopharmacy studies have noted that this degradation is worse in the months from May through September (in the northern hemisphere). Drugs in solid form are sometimes reduced to a crumbly powder, increasing the absorption rate. This change in absorption only slightly offsets the decrements in biological activity and dosing accuracy.

A few drugs move from the purse compartment into the curious toddler compartment.⁴ This transfer can have lethal results. Child-proof containers reduce movement into this compartment but themselves produce a pressure to move the drug to another, unlabeled or mislabeled container, this movement carrying its own hazards as mentioned above.

Most drugs are actively transported to the kitchen table/bathroom cabinet space (KTBC). Clearance from this space is frequently slow, and incomplete clearance is commonplace. A half-life running to several years is not unknown, especially for antibiotics. Long retention in this space leads to crumbly degradation similar to that seen in the glove box compartment. A back-up mechanism for removal from the KTBC space is movement to the ill-family-member compartment. The mechanism for this transfer can be best summarized: "When all you have is a hammer, everything looks like a nail." Under this rubric, any drug in the KTBC compartment can be seen to be a "hammer" and any illness being suffered by the family member is the "nail." Unfortunately, the hammer hits the nail at the level of chance. (Studies reporting the number needed to treat for drugs from the ill-family-member compartment average around 360 for efficacy, with the number needed to harm running about 265.) Though separately denominated, the ill-friend-compartment behaves like the ill-family-member compartment. These compartments are probably one and the same.

Summarizing some of these pre-ingestion clearance equations, we have:

$$A_{\text{pharmacy}} = ID \times 1/K_1$$

$$[KTBC] = A_{\text{pharmacy}} - (A_{\text{financial}} + A_{\text{toddler}} + K_e), \text{ where}$$

[KTBC] = kitchen table/bathroom closet concentration

ID = inscribed drug dose

A_{pharmacy} = pharmacy authorization

$A_{\text{financial}}$ = financial adjustment made by patient at pharmacy

A_{toddler} = toddler appropriation

K_1 = oscillation constant, usually taken as 0.20

K_e = elimination rate via dashboard degradation pathway

A transitional compartment is the by-the-door space. This is really a local oscillation within one compartment. On the morning of the trip to the physician's office, current drugs are moved to a flat surface by the door, so as not to be forgotten. The by-the-door location produces a reuptake inhibition by which the drug cannot be picked up again until the patient returns from the physician visit. Thus, this new position impairs short-term memory. The drugs sit in the by-the-door space while the patient is in the physician's office, then transit back to the KTBC upon the patient's return home, until the next oscillation. The carrier proteins are thought to be the same as the ones that bring the drug from the unconscious engram phase to the inscribed-drug phase at T_0 .

Diversion Kinetics

Considered from a broader vantage point, drugs that move from the inscribed to the manifest chemical state may be seen as being distributed widely in the community. In a process known as

"diversion," certain mind-altering inscribed drugs move from the pockets of pseudo-patients to other pseudo-patients for use other than what the prescribing dupe had in mind. In such a diversion the drug has a much faster distribution and a shorter half-life. This same distribution can occur in the manifest drug phase. Other drugs than those which are mind-altering diffuse into the community at a slower distribution rate, often but not invariably beginning in the household. Common sites for diffusion are the workplace and in social gatherings. Viagra may prove to be a non-mind-altering drug with an especially rapid community diffusion.

A special shunt for manifest chemical drugs is the "sample closet." The manifest chemical drug arrives here through an alternate pathway. The inscribed-drug form is proffered to the physician for batch-format delivery, requiring his signature only. Transcription errors are minimized, but this advantage is more than offset by the loss of the pharmacy-organ checkpoint. Bypassing the community pharmacy, large quantities of drugs are delivered into a special space in the physician office compartment from which location they diffuse widely to the sister-in-law of the office nurse and the niece of the receptionist. A K_1 constant can be applied here also (see Figure 1). The "sample closet" was supposed to have evolved in response to the need of physicians to form new engrams, but the degree of alternative diffusion has cast doubt on this interpretation.⁶ The sample-closet shunt has put small but definite further pressure on the AWP-deprived pharmacy organ. The physician-office organ exerts no labeling, quality, or inventory control over the sample-closet pathway, leading to frequent community uptake of drugs of less than full potency or appropriateness.

The community diffusion of manifest chemical drugs produces a circuit-closing effect; in the mind of the community is formed an engram, fixing certain connections firmly but inaccurately. Irreversible covalent bonding has, for example, so fixed antibiotics to coughs and colds that only a thermonuclear event could separate the two. These engrams become as difficult to eradicate as those from the residency training of physicians.

Figure 1 provides an algorithmic summary view of pre-ingestion pharmacokinetic modeling.

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REFERENCES

- 1 Taylor WJ, Caviness MH, eds. *A Textbook for the Clinical Application of Therapeutic Drug Monitoring*. Abbott Laboratories; 1986.
- 2 Beardon PHG, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *BMJ* 1993;307:846-848.
- 3 Krogh C, Wallner L. Prescription-filling patterns of patients in a family practice. *J Fam Pract* 1987;24:301-302.
- 4 Jacobson BJ, Rock AR, Cohn MS, Litovitz T. Accidental ingestions of oral prescription drugs: a multicenter study. *Am J Public Health* 1989;79:853-856.
- 5 Jones KW & Terrell HP. Factors in family sharing: a meta-analysis, in press, as soon as we can find one, 2004.
- 6 Morelli D, Koenigsberg MR. Sample medication dispensing in a residency practice. *J Fam Pract* 1992;34:42-48.