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Editorial

by Dr. Oscar Linares

Welcome to the first volume of the electronicPainJournal (EPJ). The EPJ is a volunteer project featuring short to medium size articles covering topics that might be of interest to prescribers who manage acute and chronic pain patients, in general, and pain practitioners, in particular. The EPJ emphasizes rational therapeutics, i.e., computational methods for drug prescribing and simulation analysis and modeling for drug dose regimen design and modification.

The EPJ as a medium for communication intends to fill a gap that exists in pain journals. While there are several pain journals that cover various aspects of pain medicines, there is no pain journal that deals with computational or clinical pharmacokinetics-based opioid prescribing. In addition, while there are several scientific journals dealing with pharmacogenomics, there is currently no journal publishing articles that attempt to integrate pharmacokinetics with pharmacogenomics. The EPJ hopes to fill this gap also.

This first volume features a range of articles aimed at reviewing first principles. For many prescribers, drug metabolism and pharmacokinetics are subjects they have not contemplated since their university days. In this sense, this issue serves as a review.

When compared to other scientific journals, publication in the EPJ is faster. Articles are reviewed by the editorial board to ensure their quality. Submissions should simply be sent to the editor in chief by email. The success of the EPJ critically depends on the articles in it, hence I want to ask all of you to submit your articles to the EPJ.

The Linares Addictive Potential Model

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Abstract The Salerian Addictive Potential (SAP) hypothesis indicates that addictive potential may be calculated as $A = E/T_{\max} \times t_{1/2}$, where A is addictive potency, E euphoric potency, $T_{\max}$(hr) is the time to reach peak plasma concentration, and $t_{1/2}$(hr) is the plasma elimination half-life. However, this approach is inconsistent with first-order linear pharmacokinetics. The units of the denominator of the equation are units of acceleration (hr^2) not speed (the first derivative). Therefore, the present contribution presents a minimal-model hypothesis for quantifying a drug's addictive potential. This model is superior to the SAP model because it is the simplest model, with the minimum number of parameters and assumptions, and it decreases variance through less loss of information.

Keywords: Clinical pharmacokinetics; dopamine; opioids; euphoria; drugs of abuse; drugs of misuse

1.1 Introduction

A mathematical model is a hypothesis defined by a set of parameters in a mathematical framework [1]. In a mathematical model, parameters or their functions may be used without regard to mechanistic aspects of the system under investigation. By contrast, in a physical model, parameters reflect physiological, pharmacological, or biochemical mechanisms. A model's parameters are the quantifiable constants, equations or functions of the model.

Recently, Salerian [2] developed a mathematical model for measuring the addictive potency of several drugs based on the Salerian Addictive Potential (SAP) score. The Salerian model improved methodology for drug addiction classification by structuring classification in a mathematical pharmacokinetics-based framework, accounting for the speed with which a drug can be absorbed and excreted from the body. Despite its benefits, use of the SAP model as an index of addictive potential is associated with several problems: (i) the SAP model takes into account both drug absorption and elimination as reflected in the $T_{\max}$ parameter, which confounds the computed value of addictive potential; (ii) in the SAP model, E, the euphoric potency of the drug, is subjectively assigned; (iii) the SAP model provides no insight into the relative contributions that absorption and elimination make to the addictive potency of a drug, when absorption and elimination are important determinants of the "high" produced by drugs of misuse; and (iv) the SAP model is inconsistent with first-order linear pharmacokinetics.

In the metabolism of drugs of misuse, confounded parameters vary together so that one cannot tease apart the relative contribution of each parameter to the observed effects. It is important to assess the relative contribution of each parameter because the direction of the effect of a confounder can lead to either an over- or under-estimate of the primary outcome measure. This mis-estimate may cause misclassification of the primary outcome measure.

Using modeling [3], the present work was undertaken to address the effect of confounding on the SAP model and to quantify more precisely the addictive potential of drugs of misuse. The present contribution presents a minimal-model hypothesis for quantifying a drug's addictive potential. This model is superior to the SAP model because it is the simplest model, with the minimum number of parameters and assumptions, and it decreases variance through less loss of information.

1.2 Theory

The SAP model [2] is described by Eq. (1.1):

$$A = \frac{E}{(T_{\max} \times t1/2)}. \tag{1.1}$$

In this model, A represents addictive potential in units of hr^{-2}, E represents euphoric potency on a scale from 1 to 5 with 5 being the most potent, $t1/2$ (hr) is the elimination half-life and $T_{\max}$(hr) is the time to peak absorption (rate of exposure) or time to peak concentration (extent of exposure) in plasma, blood or serum [2]. $T_{\max}$ is thus a hybrid pharmacokinetic parameter dependant on the fractional rate of drug absorption, (k_a hr^{-1}), into the

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Table 1.1: Drugs ranked by the Salerian Addictive Potential score A. This table presents the SAP score for drugs calculated using Eq. (1.1). Table 1.1 parallels Table 1.2 in Salerian [2] but adds clonazepam, lorazepam and heroin.

Rank	Drug	Intake Route	E	$T_{\max}$	$t_{1/2}$	A
1	Heroin	intravenous	5	0.078	1.6	39.89
2	Cocaine	inhalation	5	0.16	1.0	31.25
3	Alcohol	oral	4	0.25	1.5	10.67
4	Morphine	intravenous	4	0.16	3.0	8.33
5	Oxycontin	chewed	4	0.11	4.5	8.08
6	Nicotine	inhalation	2	0.16	2.0	6.25
7	Morphine	oral	4	0.50	3.0	2.67
8	Oxycodone NR	oral	4	0.50	3.5	2.29
9	Lorazepam	oral	4	2.00	1.0	2.00
10	Oxycodone CR	oral	4	0.50	4.5	1.78
11	Clonazepam	oral	4	2.50	1.3	1.28
12	Amphetamine Salts	oral	4	0.50	10.0	0.80
13	Methylphenidate	oral	4	1.50	4.0	0.67
14	THC	inhalation	4	0.16	72.0	0.35
15	Alprazolam	oral	4	1.50	11.2	0.24
16	Lisdexamphetamine	oral	4	3.50	12.0	0.10
17	Diazepam	oral	4	1.00	50.0	0.08
18	Buprenorphine	oral	4	2.00	26.0	0.08
19	Methadone	oral	5	1.50	55.0	0.06
20	Concerta	oral	4	7.00	10.0	0.06
21	Dronabinol	oral	4	1.00	72.0	0.06

body, as well as the fractional rate of drug elimination, (k_e hr^{-1}), from the body:

$$T_{\max} = \frac{\ln(k_a/k_e)}{(k_a - k_e)}. \tag{1.2}$$

The peak concentration, $C_{\max}$ is also a function of k_a and k_e [4]:

$$C_{\max} = \frac{k_a F D}{V_d\,(k_a - k_e)} \left(e^{-k_e T_{\max}} - e^{-k_a T_{\max}}\right), \tag{1.3}$$

where F (%) represents the bioavailability of the drug, D (mg) represents the oral dose administered, and V_d(L) represents its apparent volume of distribution.

The half-life for the absorption process, defined as the time required for half the absorbed dose to be absorbed, is expressed as

$$t_{1/2a} = \frac{\ln(2)}{k_a}, \tag{1.4}$$

where $\ln(2) \cong 0.693$. The $t_{1/2a}$ units are hours. Multiplying $t_{1/2a}$ by 5 to mark five half-lives to steady state gives the elapsed time equal to 96.875% of the absorbed dose (FD) which, for clinical purposes, represents complete absorption. Similarly, the half-life for the elimination process, expressed as

$$t_{1/2} = \frac{\ln(2)}{k_e}, \tag{1.5}$$

multiplied by 5, represents complete elimination. Thus, as shown by Eqs. (1.4) and (1.5), k_a and k_e are "unconfounded" independent predictors of drug absorption and elimination, unlike the $T_{\max}$ in Eq. (1.2).

1.3 Model Development

The SAP model given by Eq. (1.1) may be decoupled by splitting $T_{\max}$ into its independent component parts:

Table 1.2: Drugs ranked by addictive potential using the Linares addictive potential index A_L. Table 1.2 presents the drugs tabulated in Table 1.1 ranked according to A_L.

Rank	Drug	Intake Route	E	$T_{\max}$	$t_{1/2a}$	$t_{1/2}$	k_a	k_e	k_a/k_e	A_L
1	Heroin	intravenous	5	0.1	0.17	1.6	4.16	1.386	3.00	1.67
2	Concerta	oral	4	7.0	3.500	10.0	0.20	0.069	2.86	1.40
3	Methylphenidate	oral	4	1.5	0.750	4.0	0.92	0.173	5.33	0.75
4	Lisdexamphetamine	oral	4	3.5	1.750	12.0	0.40	0.058	6.86	0.58
5	Cocaine	inhalation	5	0.16	0.080	1.0	8.66	0.693	12.50	0.40
6	Alcohol	oral	4	0.25	0.125	1.5	5.54	0.462	12.00	0.33
7	Morphine	oral	4	0.5	0.250	3.0	2.77	0.231	12.00	0.33
8	Lorazepam	oral	4	2.0	1.000	1.0	0.69	0.058	12.00	0.33
9	Oxycodone NR	oral	4	0.5	0.250	3.5	2.77	0.198	14.00	0.29
10	Oxycodone CR	oral	4	0.5	0.250	4.5	2.77	0.154	18.00	0.22
11	Alprazolam	oral	4	1.5	0.750	11.2	0.92	0.062	14.93	0.27
12	Buprenorphine	oral	4	2.0	1.000	26.0	0.69	0.027	26.00	0.154
13	Clonazepam	oral	4	2.5	1.250	1.3	0.55	0.020	27.20	0.15
14	Morphine	intravenous	4	0.16	0.080	3.0	8.66	0.231	37.50	0.11
15	Amphetamine Salts	oral	4	0.5	0.250	10.0	2.77	0.069	40.00	0.10
16	Nicotine	inhalation	2	0.16	0.080	2.0	8.66	0.347	25.00	0.08
17	Methadone	oral	5	1.5	0.750	55.0	0.92	0.013	73.33	0.07
18	Diazepam	oral	4	1.0	0.750	50.0	0.92	0.014	66.67	0.06
19	Oxycontin	chewed	4	0.11	0.055	4.5	12.60	0.154	81.82	0.05
20	Dronabinol	oral	4	1.0	0.500	72.0	1.39	0.010	144.00	0.03
21	THC	inhalation	4	0.16	0.080	72.0	8.66	0.010	900.00	0.004

$$A = \frac{E}{(k_a/k_e)} \times t_{1/2}. \tag{1.6}$$

In this version of the model, A depends on both k_a and k_e. Both k_a and k_e are independent processes driven by different kinetics which cannot be ignored [5] because they quantify drug absorption and elimination. The units of Eq. (1.6) are inconsistent with those of Eq. (1.1). Although the units of Eq. (1.1) are hr^{-2} which is a unit of acceleration, the units of Eq. (1.6) are hr^{-1} which is a unit of speed.

Because a dimensionless quantity in the denominator of Eq. (1.6) is needed, the $t_{1/2}$term is dropped from the denominator in Eq. (1.6) giving

$$A_L = \frac{E}{(k_a/k_e)}, \tag{1.7}$$

where A_L represents the Linares addictive potential index. Although $T_{\max}$ is a non-compartmental model parameter, its calculation is based on a linear dynamic compartmental model that follows linear first-order kinetics [3], i.e., dC/dt, not dC^2/dt^2, which is implied by the units of Eq. (1.1). Dropping the $t_{1/2}$term from Eq. (1.6) is allowable because $t_{1/2}$measures drug elimination, which is accounted for by k_e. In addition to being both theoretically and dimensionally correct, Eq. (1.7) now proposes the simplest model hypothesis or the minimal-model for the Linares addictive potential index.

1.4 Empirical data

No "gold standard" exists for estimating the classification accuracy of addictive potential. Pepe [6] and Hagdu [7] suggest approaches to studying comparisons

Table 1.3: "Gold standard" ranking of selected drugs using values for addictive potential by adjudication by expert committee based on fact and scientific knowledge (column FSKEO) in Nutt and coworkers [11] and match-ranked by A and A_L*.

Gold Standard	FSKEO Rank	FSKEO	A Rank	A	A_L Rank	A_L
Heroin	1	3.00	1	39.89	1	1.67
Cocaine	2	2.39	2	31.25	2	0.08
Tobacco	3	2.21	3	6.25	8	0.04
Methadone	4	2.08	9	0.06	7	0.07
Alcohol	5	1.93	2	10.67	3	0.33
Benzodiazepines	6	1.83	7	0.24	4	0.27
Amphetamine	7	1.67	8	0.10	2	0.58
Cannabis	8	1.51	5	0.35	9	0.004
Methylphenidate	9	1.25	4	0.67	5	0.19

*$\boldsymbol{A}$=Salerian Addictive Potential score.
$\boldsymbol{A_L}$=Linares Addictive Potential index.

without a gold standard. One approach is to use values adjudicated by a committee of experts as the gold standard. Using this approach, Table 1.3 tabulates the drugs in reference [8] that are also used in Tables 1.1 and 1.2. The nine drugs that were common to both studies were ranked from one to nine on the basis of their addictive score settled by the expert committee [8]. The drug's A scores and A_L indices were then used to match-rank the drugs relative to their scores based on fact, scientific knowledge, and expert opinion (FSKEO) as shown in Table 1.3.

1.5 Evaluation of Models

As shown in Table 1.1, A identified heroin, cocaine, and alcohol as the highest addictive potential. By contrast, A_L ranked heroin, Concerta©, and Ritalin© as the drugs with the highest addictive potential, followed by cocaine and alcohol.

To determine the accuracy of the models while controlling for model complexity, the Akaike Information Criterion (AIC) [9] was used as a measure of information content. The lower the value of the AIC, the more statistically accurate the model because less information is lost when the model is used to describe data. The AIC was calculated as $AIC = N \times \ln(SS_R) + 2 \times P$ [10], where N is the number of drugs studied, SS_R is the sum of squared residuals calculated from the difference between the model rankings of addictive potential using A and A_L relative to the FSKEO (Table 1.3), and P is the number of parameters in the model. While the SAP model has four parameters, the Linares minimal-model (LMM) has only three parameters, which is superior given the principle of parsimony [11].

Although the SS_R was lower for the SAP model compared to the LMM (87 vs. 100, respectively), the AIC was lower for the LMM compared to the SAP model (42.8 vs. 43.7, respectively). While the lower SS_R with the SAP model indicates that it is a better model if SSR were being used as the criterion for model selection, it is the AIC that provides the better model selection criterion because it considers both accuracy and parsimony.

Thus, the LMM more accurately describes the observations and postulates the simplest model hypothesis for addictive potential.

1.6 Discussion

What is offered here is not an ironclad rule for computing a drug's addictive potential, but rather a parsimonious hypothesis for its computation that must be judiciously applied.

Since modeling is rarely used in the absence of prior information, a special measure of addictive potential was derived by tailoring the SAP model [2]. The LMM dissociates the independent k_a and k_e components from $T_{\max}$ and drops the $t_{1/2}$ term from the denominator of the SAP model, giving rise to the simpler LMM represented by Eq. 1.7. Because no gold-standard exists to compare the models, Eqs. (1.1) and (1.7), values for addictive potential adjudicated by a committee of

experts [8] were used to compare the models as shown in Table 1.3.

Using the AIC as an objective model selection criterion [12], compared to the SAP model, the LMM, Eq. (1.7), emerged as the simplest model with the smallest number of parameters that captures the important pharmacokinetic determinants of addictive potential, k_a and k_e, reflected in A_L. Because it only depends on independent parameters, A_L, is a clean, unconfounded index of addictive potential.

As shown by Eqs. (1.2) and (1.3), both $T_{\max}$ and $C_{\max}$ are confounded parameters because both depend on k_a and k_e. Basson and coworkers [13] found that $C_{\max}$, but not $T_{\max}$ was confounded. However, Basson and coworkers did not dissociate $T_{\max}$ into its independent components, as was done in the present contribution in order to create a simpler model.

Salerian [2] suggests that the euphoric potency of a drug may be related to its extent of exposure ($C_{\max}$) to the neuronal milieu of the prefrontal cortex through mediation of dopaminergic system function. Positron emission tomographic (PET) imaging of the human brain in drug misuse individuals [14], reveals that although drugs of misuse are associated with rapid increases in central extracellular dopamine levels, these individuals experience a marked decrease in central dopamine release and D2 dopamine receptor number. These effects have been found to persist months after detoxification [14]. The reduction in dopamine release may represent the central inhibition of dopamine outflow in the setting of higher intrasynaptic dopamine concentration. In addition to local feedback mechanisms, the decreased dopamine outflow may be mediated by central actions such as pathways involving α_2-adrenergic receptors [15].

Because central dopamine outflow is reduced, a concomitant compensatory decrease in central dopamine clearance is needed to maintain dopamine levels elevated in the synaptic axoplasm. This decrease in central dopamine clearance may explain the observed decrease in dopamine D2 receptor number, which may in turn determine a drug's euphoric potency. Volkow and associates [16, 17] have observed a reduced clearance of methlphenidate HCl from the brain. This is an important finding because it suggests addictive potential may be related more to how slowly a drug is cleared from the synaptic axoplasma, where as the "euphoric high," may be related more to how fast the drug reaches peak concentration ($C_{\max}$) in the synaptic axoplasm. LMM's prediction that a drug's $C_{\max}$ may be a reasonable biomarker of euphorigenic potency is consistent with Salerian's reasoning and illustrates how LMM can be used in its predictive capacity. However, the neuronal dopaminergic mechanisms involved in the euphoric response to drugs of misuse is a complex process [18] requiring further study.

1.7 Conclusion

The LMM is superior to the SAP model because: (i) LMM is the simplest model with the minimum number of parameters and assumptions; (ii) LMM is associated with lower AIC; and (iii) unlike the SAP model, LMM is dimensionally and theoretically correct. The LMM represents a working hypothesis. Validation through alternate independent approaches including the design of experiments to test the model is needed. Furthermore, by the use of qualitatively different experimental techniques, new types of data may be derived which are beyond the predictive domain of the model. Under these circumstances, a new more extensive model would have to be proposed that could provide more precise information and a more complete description of addictive potential. But, regarding assessing addictive potential, LMM appears to be useful for practical applications because it provides accurate indices of addictive potential compared to adjudicated values from a panel of experts. The LMM thus provides an improved approach for the quantitative study of addiction potential in humans.

1.8 Future Directions

Salient future directions involve accounting for inter-individual differences in addictive potential. The LMM is a not an individual-specific model. For example, the model cannot account for individual-specific genetic and psychosocial influences affecting addiction. In addition, the model does not take into account individual pharmacokinetic traits that may predispose a particular individual, more than another, to opioid addiction.

In the current work, k_e was calculated using Eq. (1.5). However, to account for differences among individuals in drug extent of exposure, reflected by the apparent volume of distribution (V_dL/kg), and rate of exposure, reflected by the clearance rate ($C\ L$ L/min/kg), Eq. (1.5) can alternatively be expressed as Mehvar notes [19]:

$$t_{1/2} = \frac{0.693 \times V_d}{CL} \tag{1.8}$$

Further experimental work is being done with Eq. (1.8) to determine whether it can, together with the LMM, predict individual-specific addictive potential. Other work involves encoding ke with pharmacogenetic information (PGI), where ke is embedded within the framework of some controlling PGI function. The inclusion of PGI would add more individual-based specificity to the computation of addictive potential and potentially increase its predictive value.

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Compartment Analysis with R

One-Compartment Model

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Abstract In this article we study clinical pharmacokinetics using the NIH-WinSAAM software.

Keywords: Compartmental analysis; pharmacokinetics; WinSAAM; modeling

2.1 Introduction

To determine whether differences in neuronal reuptake contribute to age-related changes of sympathetic nervous system activity, we compared norepinephrine (NE) release and metabolism during [3H]NE infusion and decay in six young (age 126 yr) and seven older (age 61-73 yr) healthy nonobese subjects. Subjects were studied on a control day and on a separate day after desipramine (DMI; 125 mg orally), a neuronal reuptake blocker. Compartmental analysis of plasma NE specific activity was used to determine several NE kinetic parameters.

Plasma NE levels and NE spillover rates were higher in the elderly. Although plasma NE was unaffected by DMI in both age groups, both the metabolic clearance rate of NE from plasma and the rate of NE spillover into plasma fell in young and older groups during DMI. Furthermore, DMI dramatically lowered the mass of NE in the extravascular compartment and the rate of NE entry into the extravascular compartment. Thus neuronal uptake blockade has major effects on NE release as well as NE metabolism in humans. However, age-related differences in NE kinetics cannot be explained by differences in neuronal uptake.

Plasma NE levels and NE spillover rates were higher in the elderly. Although plasma NE was unaffected by DMI in both age groups, both the metabolic clearance rate of NE from plasma and the rate of NE spillover into plasma fell in young and older groups during DMI. Furthermore, DMI dramatically lowered the mass of NE in the extravascular compartment and the rate of NE entry into the extravascular compartment. Thus neuronal uptake blockade has major effects on NE release as well as NE metabolism in humans. However, age-related differences in NE kinetics cannot be explained by differences in neuronal uptake.

Alterations of sympathetic nervous system function have been implicated in impaired adaptive circulatory mechanisms in aging (25). Plasma levels of norepinephrine (NE), the major neurotransmitter of the sympathetic nervous system in humans, are higher in the elderly not only at rest (42) but also during the stresses of upright posture, exercise, glucose ingestion, and a mental stress test (25, 41). The increase in plasma NE in the elderly is due to both diminished NE clearance from the circulation and increased appearance of NE in the plasma (39). The relative contributions of release and removal mechanisms to the level of NE in plasma have been previously assessed primarily by use of tritiated NE ([3H]NE) to estimate plasma NE kinetics. We have recently employed compartmental analysis to provide further information about NE kinetics in humans, particularly about NE kinetics in a large extravascular compartment (26, 27, 35).

NE is cleared from the neuroeffector junction by neuronal (uptake 1) and nonneuronal (uptake 2) mechanisms. Disturbances in these clearance mechanisms may have pathogenetic significance in cardiovascular disease states. For example, in some hypertensive patients, defective uptake 1 has been reported (12, 21). The present study was designed to determine whether impaired neuronal reuptake contributes to the age-related changes of NE kinetics. An oral dose of 125 mg of a tricyclic antidepressant, desipramine (DMI), has been used previously to block neuronal reuptake in humans (22). In the present study, DMI was given to both young and elderly subjects before tracer NE infusion to separate the effects of uptakes 1 and 2 on NE metabolism. This study demonstrates major effects of DMI on NE re-

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lease and metabolism and qualitatively similar effects of DMI on young and old humans.

2.2 Methods

Protocol. Six young subjects (5 men and 1 woman) 19- 26 yr of age and seven older subjects (3 men and 4 women) 61-73 yr of age were studied. All were healthy and within 30Life Insurance tables). There was no difference in body weight between the young and old groups (112 t 4 vs. 109 t 4any medication, and all were screened with a medical history, physical examination, and routine clinical blood tests to ensure that they were without any clinical condition known to affect catecholamine metabolism. The subjects were prohibited from the use of known modulators of catecholamine release and metabolism, including nicotine, caffeine, and marijuana, for 12 h before the studies. The protocols were approved by the University of Michigan Human Use and Radiation Control Committees. All subjects were studied in the supine position after an overnight fast on 2 consecutive days at the University of Michigan Hospitals.

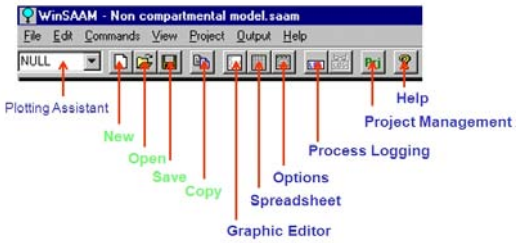

Figure 2.1: Menu items and toolbar buttons.

A control NE kinetics study was performed on the 1st day and a second NE kinetics study was performed on the following day 3 h after oral ingestion of 125 mg of DMI (Norpramin, desipramine hydrochloride, Merrell Dow Pharmaceuticals, Cincinnati, OH). The study protocol (Fig. 2.1) was identical on both days. A fixed sequential protocol design was chosen to avoid the possibility of a carryover effect of DMI to the following day if sequence randomization had been used. We have not observed a sequence effect in sequential NE kinetic studies done on the same day (26) or in baseline studies done 4 wk apart in a double-blind placebo controlled crossover design (32, 34).

An intravenous catheter was placed in an antecubital vein of one arm for infusion of [3H]NE. In the contralatera1 arm, a scalp vein needle was inserted retro-

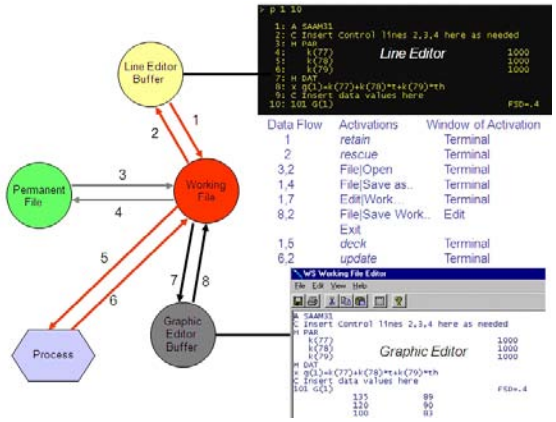

Figure 2.2: Menu items and toolbar buttons.

gradely into a dorsal vein of the hand, which was placed in a warming box at 60C to obtain arterialized blood samples. This approach has been used for studying the kinetics of a variety of substrates and hormones (17, 28) and has previously been validated for catecholamines (5, 38). The catheters were kept patent with 0.45saline.

The first 1 ml of blood sampled was discarded at each sampling time. Subjects received infusions of L-[ring-2,5,6-3H]NE (sp act 40.4 Ci/mmol; Du Pont-New England Nuclear, Boston, MA) at an infusion rate of -0.35 &i l min. mm2 for 60 min using a syringe pump (Harvard Apparatus, S. Natick, MA). Infusates contained 1 mg/ml ascorbic acid to prevent oxidation of NE. Arterialized blood samples (10 ml) were collected at 40, 50, and 60 min during [3H]NE infusion for measurement of steady-state [3H]NE and plasma NE concentrations. A sample was also obtained for measurement of plasma DMI concentrations on the study day. Blood pressure and heart rate measurements were obtained after blood withdrawal at 40, 50, and 60 min during the [3H]NE infusion (automated sphygmomanometer BP203NA, Air Shields, Hatboro, PA).

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WinSAAM: Software for Pharmacokinetic Modeling

Oscar A. Linares, Darko Stefanovski and Ray C. Boston

Abstract Compartmental modeling is the backbone of pharmacokinetics and its has contributed substantially to our understanding of normal and abnormal system states in living and nonliving systems.

3.1 Introduction

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs in the body and compartmental modeling is the backbone of pharmacokinetics. Compartmental modeling has a long history of application in the study of metabolism and pharmacokinetics in humans [2, 3, 4]. Efficient and effective computational pharmacokinetics [5] calls for an array of integrated computer modeling tools for knowledge discovery, optimum dose regimen design, and pharmacokinetic system identification. The SAAM (Simulation, Analysis, And Modeling) software is one such system which has evolved over 50 years and is underpinned by the pioneering contributions of Mones Berman at the National Institutes of Health (NIH),
Bethesda, MD [6, 7, 8]. WinSAAM [9, 10] is the direct descendent of SAAM, albeit with considerable enhancement of capacity and performance. The evolutionary nature of the software has led to a consistent methodology so that investigators can dynamically explore systems and processes using pharmacokinetic models in real-time. Although WinSAAM is software for compartmental modeling, the backbone of pharmacokinetics, there remains some confusion with regard to WinSAAM's scope of application in pharmacokinetic work [12].

This paper demonstrates WinSAAM use for pharmacokinetic modeling and parameter estimation (WinSAAM is free software [`http://www.winsaam.com`]). The paper thus serves as a user and applications manual for WinSAAM in general, and pharmacokinetic data analysis with WinSAAM, in particular. The mathematical formulation and solution of compartmental and pharmacokinetic models are discussed in detail in texts by Norwich [14], Lassen & Perl [15], Godfrey [16], Brown [1], Jacquez [3], Cobelli, Foster, and Toffolo [13], Gibaldi and Perrier [17], Bates and Watts [18], and Seber and Wild [19], and the papers by Jacquez and Simon [20, 21]. General strategies for modeling with compartments have been presented by Jacquez [22] and Wastney et. al. [23]. For ease of exposition, derivations of mathematical solutions are not included. The reader is referred to the references for details. Certain applications may require the use of nonstandard models for which the reader will be required to consult other sources to derive his or her own solutions. This paper emphasizes the principles underlying the WinSAAM solutions to pharmacokinetic models and their interpretation.

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3.2 Background

Brief History

In 1956, Berman and Shoenfeld [24] and Mones Berman in his PhD thesis [25] developed a mathematical approach to quantify radioisotopic experiments in terms of linear constant coefficient differential equations reflected by compartments. Shortly thereafter, Berman developed the Simulation, Analysis, And Modeling (SAAM) software for compartmental analysis [6, 7]. In the late 70's and early 80's, Boston optimized the SAAM software and developed its user–interface [12]. The latter gave birth to computer-assisted computational compartmental modeling and allowed its wide application in biology and medicine. Since its development, the SAAM software series has been used for experimental kinetic data analysis in over 1000 peer reviewed scientific publications in the literature.

Using WinSAAM

WINSAAM INTERFACE

Figure 3.1 shows WinSAAM's menu items and toolbar buttons interface. To start a new problem, select `FILE|NEW` from the menu. To work on an existing problem, select `FILE|OPEN`. This opens a WinSAAM text input file (a ASCII text file with extension *.saam) and makes it the *working* file.

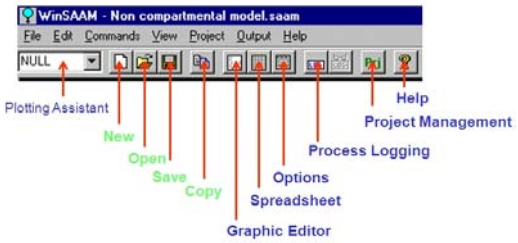

Figure 3.1: Menu items and toolbar buttons.

MODELING CONSTRUCTS

WinSAAM has its own dictionary of modeling constructs (also called operational units) which allow the user to sketch a proposed compartmental/pharmacokinetic model, and from that sketch, enter the model directly into the software (Figure 3.1).

3.3 PHARMACOKINETIC MODELING

INTRODUCTION

Pharmacokinetic modeling is a convenient tool to analyze drug data. When the distribution of drug in one state is distinguishable from the distribution of drug in another state, i.e., the drug undergoes homogeneous distribution, and/or redistribution and partitioning into one or more regions in the body, in this case, the time-course of the concentration of drug in the body can be described by a set of simultaneous ordinary differential equations. We develop both the basic theory and nomenclature for this paper in parallel with the nomenclature of the SAAM dictionary, i.e., the language used to describe a model to WinSAAM.

KINETIC PROCESSES

The time-scale for the processes involved in the transfer of drug into, within, and out of the body is finite, and it is mostly due to the time it takes for drug to transfer across body membranes. For example, the rate-limiting step to absorption of drug from the gastrointestinal tract is the transfer of drug across the epithelial tissue of the gastrointestinal tract, whereas the elimination of drug from the body may be slowed due to glomerular filtration and transport across Bowman's capsule membranes. Other potential rate-limiting processes include distribution of drug to body organs and tissues, tubular reabsorption in the kidney, enterohepatic cycling, hepato-portal circulation and biochemical reactions.

Drug transport across rate-limiting barriers such as the cell membrane is fundamental to pharmacokinetics. A cell membrane normally refers to the plasma membrane that surrounds the cytoplasm of a cell and forms the cell boundary. The cell membrane consists of a lipid bilayer with embedded proteins. Depending on the membrane's location and role in the body, lipids can make up anywhere from 20 to 80 percent of the membrane, with the remainder being proteins. Lipids generally give membranes their flexibility. Cholesterol is a type of lipid that, by contrast, helps stiffen the membranes of mammalian cells.

The cell membrane regulates what enters and leaves the cell, maintains the correct intracellular pH level, and provides a means of separating charges so that the cell can, for example, generate the energy-carrying molecule adenosine triphosphate. Proteins transmit chemical messages into the cell, and they also monitor and maintain the cell's chemical climate. On the outside of cell membranes, attached to some of the proteins and lipids, are chains of sugar molecules that help each cell type do its job.

The cell membrane is both a physical and chemical barrier which defines the boundary between the individual and its environment. Its origin is intimately connected with the origin of life as we know it. Cell membranes are sheet-like structures, typically 7.5 nm thick. They consist mainly of lipid and protein, and may also contain sugars. Membrane lipids are relatively small molecules that have both hydrophilic and hydrophobic properties. Specific proteins mediate specific functions in membranes, e.g., transport and energy generation. Membranes are asymmetric fluid structures.

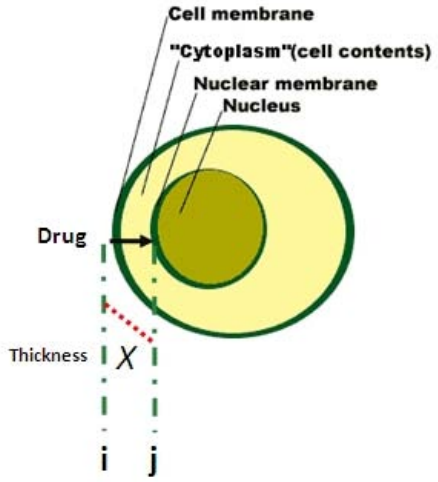

Figure 3.2: Membrane.

EXPONENTIAL MODELS

Selecting the "best" model among a set of multiexponential models of increasing dimension is a common problem in pharmacokinetics because the solution of the linear differential equations of pharmacokinetic models all turn out to be polyexponential in form.

Therefore, the integrated differential equations can be generalized by Equation 3.1,

$$C(t_k) = \sum_{i=1}^{n} A_i e^{-L_i t_k} + e_k, \tag{3.1}$$

where $C(t_k)$ is drug concentration over time, A_i and L_i are unknown constant parameters corresponding to eigenvector and eigenvalue pairs, respectively, and e_k is the measurement error at each discrete time point t_k. The data are usually fitted using weighted-least squares [27, 28, 29].

The number of compartments in a compartmental model are determined by the number of exponential terms in Equation 3.1. Models with three or more exponential terms (compartments) may be configured in different ways, leading to different possible solutions, not all of which may be identifiable [13]. For this reason, pharmacokinetic models involving three or more exponential terms are not common and are motivated more on a statistical rather than a biological basis [31].

The exponential model provides a convenient model for statistical analysis, but will be difficult to interpret in terms of simple compartmental models when n is moderately large. Multiexponential models of the form given by Equation 3.1 arising as solutions to compartmental systems may also be subject to certain constraints.

Following first-order kinetics, the amount $F_1(t)$ of drug in the central compartment satisfies the following differential equation,

$$\frac{dF_1(t)}{dt} = -k_e F_1(t). \tag{3.2}$$

Since $F_1(0) = D$, the solution to Equation 3.2 is

$$F_1(t) = De^{-k_e t}. \tag{3.3}$$

Assuming the drug is distributed uniformly throughout the apparent volume of distribution V_1, Equation 3.3 can be divided by V_1 to obtain

$$C_1(t) = Ae^{-\alpha t}, \tag{3.4}$$

where $C_1(t)$ denotes the concentration of drug in the central compartment equal to $A = D/V_1$ and $\alpha = k_e$. Linearizing Equation 3.4 gives

$$\ln C_1(t) = \ln A - \alpha t. \tag{3.5}$$

Thus a semi-logarithmic plot of concentration $C_1(t)$ over time t plots a straight line.

Second, now suppose that the drug of interest is administered orally. The amount of drug $F_0(t)$ present in the gastrointestinal tract satisfies the following differential equation:

$$\frac{dF_0(t)}{dt} = -k_a F_0 t, \tag{3.6}$$

where k_a denotes the fractional transfer rate coefficient for gastrointestinal absorption. Thus, for oral dosing, $F_1(t)$ is given by

$$\frac{dF_1(t)}{dt} = k_a F_0 t - k_e F_1(t). \tag{3.7}$$

Equations 3.6 and 3.7 can be solved simultaneously using Laplace transforms to obtain

$$F_1(t) = \frac{Dk_a}{(k_a - k_e)} \left(e^{-k_e t} - e^{-k_a t}\right), \tag{3.8}$$

iff $k_a \neq k_e$. Dividing Equation 3.8 by the apparent volume of distribution V_1 gives

$$C_1(t) = A\left(e^{-\alpha t} - e^{-\beta t}\right) \tag{3.9}$$

where $A = Dk_a \left[(k_a - k_e) V_1\right]^{-1}$, $\alpha = k_e$ and $\beta = k_a$. A semi-logarithmic plot of $C_1(t)$ versus t has a terminal linear component with slope equal to α.

Lastly, if the drug is administered by constant infusion, drug is delivered into the central compartment at an essentially constant rate equal to k_0, with

$$\frac{dF_1(t)}{dt} = k_0 - k_e F_1(t). \tag{3.10}$$

Integration of Equation 3.10 and division by the apparent volume of distribution (V_1) gives

$$C_1(t) = A\left(1 - e^{-k_e t}\right), \tag{3.11}$$

where $A = \frac{k_0}{[k_e \cdot V_1]}$.

Two-Compartment Model: If the one compartment model fails to provide an adequate fit to the data, two compartment models may be entertained. For example, consider the two-compartment model in Figure 3.2 Panel B. Lets apply a single intravenous dose of drug. Then, the amounts of drug present in the central and peripheral compartments, $F_1(t)$ and $F_2(t)$, satisfy

$$\begin{aligned} \tfrac{dF_1(t)}{dt} &= -\left(k_e + k_{21}\right) F_1(t) + k_{12} F_2(t) + D \\ \tfrac{dF_2(t)}{dt} &= k_{21} F_1(t) - k_{12} F_2(t) \end{aligned} \tag{3.12}$$

where k_e is the fractional elimination rate constant from the central compartment and k_{21} and k_{12} are intercompartmental fractional rates of drug transfer between the central and peripheral compartments, respectively. The solution to Equation 3.12 is given by

$$\begin{aligned} F_1(t) &= \tfrac{D}{(\beta - \alpha)} \left[\left(k_{12} - \alpha\right) e^{-\alpha t} - \left(k_{21} - \beta\right) e^{-\beta t}\right] \\ F_2(t) &= \tfrac{Dk_{12}}{(\beta - \alpha)} \left(e^{-\alpha t} - e^{-\beta t}\right) \end{aligned} \tag{3.13}$$

where α and β satisfy the equation

$$\alpha + \beta = k_{21} + k_{12} + k_e \tag{3.14}$$

and

$$\alpha\beta = k_{12} k_{01}. \tag{3.15}$$

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