Bioavailability Assessment under Quasi- and Nonsteady-State Conditions I: Theoretical Considerations

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Abstract □ A strategy was devised to permit bioavailability estimations at quasi- and nonsteady states. The proposed method retains most attributes of a steady-state comparison without being burdened by its protractiveness. The only necessary requirements are that drug disposition obeys linear kinetics and that succeeding doses are administered during the log-linear phase free from the influence of continuing absorption.

Keyphrases □ Bioavailability—estimations under quasi- and nonsteady states, theoretical considerations and equations □ Drug accumulation under quasi- and nonsteady-state conditions—bioavailability estimations, theory and equations

An accepted method of assessing the relative bioavailability of dosage forms is to compare their mean plasma concentrations with those of a reference over a comparable dosage interval at steady state. The theoretical basis for this kind of comparison is analogous to that of comparing total areas under the plasma concentration curve in single-dose studies (1). In either case, the underlying assumptions are that plasma clearance is not concentration dependent and is constant between treatments.

Implicit in the choice of steady-state measurements is that there will be drug accumulation for the specified dosage regimen. Relative to single-dose studies, the steady-state approach has several obvious advantages. First, fewer data points are required because the time course of change in plasma concentrations is less precipitous and sampling times are bounded by the dosage interval. Second, plasma concentrations are higher. Third, the method is model independent so long as drug disposition obeys linear kinetics. The main disadvantage is that the clinical aspects are much more difficult to control and execute. It may take days or even weeks to achieve steady state. In any protracted study, the potential for lapses in subject compliance increases with time.

Unfortunately, many factors that lend support to steady-state measurements also prolong the clinical phase. Plasma half-life, $t_{1/2}$, is by far the most important parameter in drug accumulation. With increasing $t_{1/2}$, the extent of accumulation increases for a given dosage regimen, the differences between peak and trough plasma concentrations are diminished, and the plasma time course is less sensitive to the effect of variations in absorption rates.

Provided that one is not attempting to demonstrate timed-release properties, a long half-life tends to make steady-state studies more attractive. On the other hand, the study becomes more unwieldy because the time to achieve steady state also increases with increasing $t_{1/2}$. Additionally, prudent planning dictates that the longest $t_{1/2}$ among individuals should be accommodated, which simply means that the best designed studies must also be the most time consuming.

Thus, even though drug accumulation can be anticipated, the steady-state option may not always be a practical alternative to single-dose comparisons. The purpose of this article is to propose an alternative strategy to utilize the obvious advantages of drug accumulation in bioavailability assessment.

THEORETICAL

The overall strategy is to effect sufficient drug accumulation to facilitate an assessment of bioavailability without unduly prolonging the clinical phase of the study.

For a drug obeying one-compartment model kinetics, it has been shown (1–3) that the mean plasma level (the first *noncentral moment* over τ) following the administration of a fixed dose at equal time intervals is estimated by:

$$\bar{C}p^{(ss)} = \frac{FD}{\tau k_e V_d} \qquad \text{(Eq. 1)}$$

and:

$$\bar{C}p^{(i)} = \frac{k_a FD}{\tau V_d (k_e - k_a)}\left[\frac{(1 - e^{-ik_a\tau})}{k_a} - \frac{(1 - e^{-ik_e\tau})}{k_e}\right] \qquad \text{(Eq. 2)}$$

where $\bar{C}p^{(ss)}$ and $\bar{C}p^{(i)}$ are the mean plasma concentration at steady state and at the ith dose, respectively, after repeated administration of the drug at interval τ; k_a and k_e are first-order rate constants for absorption and elimination; V_d is the apparent volume of distribution; and F is the fraction of the dose, D, absorbed.

The extent and rate of drug accumulation may be calculated by:

$$\bar{C}p^{(ss)} = \frac{(k_e - k_a)\bar{C}p^{(i)}}{k_e(1 - e^{-ik_a\tau}) - k_a(1 - e^{-ik_e\tau})} \qquad \text{(Eq. 3)}$$

and:

$$\left[1 - \frac{\bar{C}p^{(i)}}{\bar{C}p^{(ss)}}\right] = \frac{k_e}{k_e - k_a}e^{-ik_a\tau} - \frac{k_a}{k_e - k_a}e^{-ik_e\tau} \qquad \text{(Eq. 4)}$$

When $k_a \gg k_e$, Eqs. 3 and 4 may be further simplified to:

$$\bar{C}p^{(ss)} \cong \frac{\bar{C}p^{(i)}}{1 - e^{-ik_e\tau}} \qquad \text{(Eq. 5)}$$

and:

$$\ln\left[1 - \frac{\bar{C}p^{(i)}}{\bar{C}p^{(ss)}}\right] \cong -k_e(i\tau) \qquad \text{(Eq. 6)}$$

Defining the half-time for accumulation, $(i\tau)_{1/2}$, as the time required to reach 50% of steady state, *i.e.*, when $\bar{C}p^{(i)} = \bar{C}p^{(ss)}/2$, one obtains:

$$(i\tau)_{1/2} \cong \frac{\ln 2}{k_e} = (t_{1/2})_e \qquad \text{(Eq. 7)}$$

Thus, the half-time for accumulation is approximately equal to the half-life for elimination. Equation 7 represents the limiting case described by van Rossum (3).

Analogous expressions for a general N-compartment mammilla-

ry model with first-order absorption are:

$$\bar{C}p^{(i)} = \frac{k_a F D}{\tau V_1}\left[\frac{(1-e^{-ik_a\tau})\prod_{j=2}^{N}(E_j-k_a)}{k_a(\alpha-k_a)(\beta-k_a)\ldots(\psi-k_a)} + \frac{(1-e^{-i\alpha\tau})\prod_{j=2}^{N}(E_j-\alpha)}{\alpha(k_a-\alpha)(\beta-\alpha)\ldots(\psi-\alpha)} + \cdots + \frac{(1-e^{-i\psi\tau})\prod_{j=2}^{N}(E_j-\psi)}{\psi(k_a-\psi)(\alpha-\psi)\ldots(\chi-\psi)}\right] \quad \text{(Eq. 8)}$$

$$\bar{C}p^{(ss)} = \frac{FD\Pi_j E_j}{\tau V_1 \alpha\beta\ldots\psi} \quad \text{(Eq. 9)}$$

where E_j is the sum of exit rate constants from compartment $j = 2, 3, \ldots, N$; $\alpha, \beta, \ldots, \psi$ are the hybrid rate constants, of which there are N in number; and V_1 is the apparent volume of distribution for the central compartment. Their derivation is given in the *Appendix*. It can be seen that Eqs. 1–7 are for the special case where $N = 1$.

One can define ω as the smallest plasma decay constant and V_0 as an operational constant such that ωV_0 is an estimate of body drug clearance. If ω is much smaller (say, one-fifth or less) than any exit rate constant, E_j, and the next larger hybrid constant, including k_a, then:

$$\bar{C}p^{(ss)} \cong \frac{\bar{C}p^{(i)}}{1-e^{-i\omega\tau}} \quad \text{(Eq. 10)}$$

$$\ln\left[1-\frac{\bar{C}p^{(i)}}{\bar{C}p^{(ss)}}\right] \cong -\omega(i\tau) \quad \text{(Eq. 11)}$$

$$(i\tau)_{1/2} \cong \frac{\ln 2}{\omega} = (t_{1/2})_\omega \quad \text{(Eq. 12)}$$

and combining Eqs. 9 and 10:

$$\bar{C}p^{(i)} = \frac{FD\Pi_j E_j}{\tau V_1 \alpha\beta\ldots\omega}(1-e^{-i\omega\tau}) = \frac{FD}{\tau\omega V_0}(1-e^{-i\omega\tau}) \quad \text{(Eq. 13)}$$

providing τ is chosen such that succeeding doses are administered during the log-linear phase (see *Appendix*).

From the foregoing, it is evident that the most important parameter in drug accumulation is the slowest rate constant for plasma decay, *i.e.*, the terminal slope.

Suppose two treatments of the same drug were to be compared by administering sequentially l doses of formulation x followed immediately by m doses of formulation y according to the same dosage regimen. If conditions for Eq. 10 are met, then:

$$\bar{C}p^{(l)} = \frac{F_x D}{\tau\omega V_0}(1-e^{-l\omega\tau}) \quad \text{(Eq. 14)}$$

and:

$$\bar{C}p^{(m+l)} = \frac{D}{\tau\omega V_0}\left[F_x e^{-m\omega\tau}(1-e^{-l\omega\tau}) + F_y(1-e^{-m\omega\tau})\right] \quad \text{(Eq. 15)}$$

where $\bar{C}p^{(l)}$ and $\bar{C}p^{(m+l)}$ are the observed mean plasma levels during the lth and $(m+l)$th dosage intervals, respectively; and F_x and F_y are the fractions of dose absorbed from formulations x and y, respectively. Implicit in Eqs. 14 and 15 are that ω remains constant, but k_a and F may differ between treatments. (See *Appendix* for derivation.)

The relative bioavailability of formulation y with respect to formulation x can be estimated by solving Eqs. 14 and 15:

$$\frac{F_y}{F_x} = \left[\frac{\bar{C}p^{(m+l)}}{\bar{C}p^{(l)}} - e^{-m\omega\tau}\right]\frac{(1-e^{-l\omega\tau})}{(1-e^{-m\omega\tau})} \quad \text{(Eq. 16)}$$

which collapses to the usual expression for relative bioavailability at steady state; *i.e.*, when $l \to \infty$ and $m \to \infty$:

$$\frac{F_y}{F_x} = \frac{[\bar{C}p^{(ss)}]_y}{[\bar{C}p^{(ss)}]_x} \quad \text{(Eq. 17)}$$

These considerations can be easily extended to accommodate three or more treatments. For example, if treatment y were followed immediately by n doses of treatment z, then:

$$\frac{F_z}{F_x} = \left[\frac{\bar{C}p^{(n+m+l)}}{\bar{C}p^{(l)}} - \frac{\bar{C}p^{(m+l)}e^{-n\omega\tau}}{\bar{C}p^{(l)}}\right]\frac{(1-e^{-l\omega\tau})}{(1-e^{-n\omega\tau})} \quad \text{(Eq. 18)}$$

In the interest of clarity, Eqs. 13, 16, and 18 have been derived with the assumption that the following simplifying conditions prevail: *(a)* the same dosage is administered repetitively for a given treatment, *(b)* the same dosage regimen is followed for all treatments, *(c)* the time intervals between successive doses are uniform throughout, *(d)* there are no discontinuities (extended "washout" periods) between treatments, *(e)* the terminal half-life for a given subject remains constant, *(f)* body drug clearance remains constant, and *(g)* succeeding doses are administered during the log-linear phase which is not influenced by continuing absorption.

Subsequent discussion will attempt to show that most, if not all, of these conditions can be modified, verified, or circumvented through appropriate experimental design and/or data analysis.

DISCUSSION

Experimental strategies for bioavailability estimation have been almost exclusively limited to comparisons following single doses or at steady state. In general, multiple-dose studies are considered only when useful accumulations can be realized through some convenient dosage regimen. However, the attainment of steady state may require an unacceptably long time. As already illustrated, most advantages of multiple-dose comparisons can be incorporated into bioavailability studies without the need to achieve steady state after each treatment. Basically, the proposed method evolves from the observation that in a linear system the incremental change in drug accumulation is largest, and therefore most useful, in the initial, nonsteady-state region.

Implicit in all bioavailability comparisons is the assumption that the observed data following a given dose are a measure of the expected performance of the administered dosage form. The task is one of acquiring a sufficient number of random samples to permit conclusions within a prescribed degree of confidence. Variability in treatment performance is generally regarded to be greater between than within subjects; hence, crossover comparisons are preferred for precision and economy. But even in crossover studies, within subject comparisons of plasma concentrations and urinary recoveries *per se* may be influenced by variations in drug disposition between treatments.

It is evident that experimental designs should include provisions to compensate for possible changes in drug distribution and elimination. Several possibilities for verifying internal consistency in single-dose comparisons were suggested (4). In multiple-dose comparisons, the observed changes in distribution and/or elimination may be considered as random samples of their mean values over the entire time course of the respective treatments. Adjustments, if necessary, are construed to be applied to their respective means in the same sense that the resultant estimates of bioavailability are measures of mean performances.

Experimentally, the direct application of Eqs. 16 and 18 calls for estimates of mean plasma concentration over the last dosage interval for each test preparation and an estimate of ω. Conceptually, what is being attempted is simply a comparison among $\bar{C}p^{(ss)}$ values, each projected from an observed mean plasma concentration at quasi- or nonsteady state, $\bar{C}p^{(i)}$. In other words, bioavailability estimation by the proposed method is analogous to comparing $\bar{C}p^{(ss)}$. For example, $[\bar{C}p^{(ss)}]_x$ for the first treatment is project-

ed from $\bar{C}p^{(l)}$ by Eq. 10, $[\bar{C}p^{(ss)}]_y$ for the second treatment is calculated from $\bar{C}p^{(m+l)}$ by first correcting for the residual contribution due to $\bar{C}p^{(l)}$, and so on. Therefore, the validity of the method is dependent on the accuracy to which $\bar{C}p^{(ss)}$ can be estimated from $\bar{C}p^{(i)}$.

All of the dosage regimen constraints embodied in the derivation of Eqs. 16 and 18 are nonsubstantive, provided that there is an accurate accounting of the dosing sequence. That is to say, the dose and the dosage intervals for the various treatments need not be uniform throughout. Once having estimated F/V_0 through $\bar{C}p^{(ss)}$ for some treatment, it can be compared with that projected from $\bar{C}p^{(i)}$ for all other treatments regardless of how they are given. The sampling periods need not be confined to the last dose of each treatment nor to a single estimate of $\bar{C}p^{(i)}$ per treatment. Dosages may be skipped to permit more extensive sampling during the log-linear phase.

Unlike the extent of drug accumulation at steady state, the predicted time course of accumulation is more or less model dependent. The rate of accumulation approaches model independence when: *(a)* ω is much smaller than E_j, *(b)* ω is much smaller than the next larger eigenvalue, *(c)* succeeding doses are administered during the log-linear phase, and *(d)* the terminal slope is not k_a. From the prior knowledge of drug disposition and from the nature of the dosage forms, it should be possible to discern whether any of these cited conditions is likely to be satisfied. The first is most ambiguous in that E_j's are model-dependent parameters which can assume a wide range of values, albeit always greater than ω, depending on how the model is depicted. However, the degree of uncertainty is no worse than that incurred in any other kinetic method of bioavailability assessment where the model and the disposition parameters are assumed to be constant between treatments in a given subject.

The second and third conditions can be easily verified and accommodated in the experimental design. If absorption is, or is suspected to be, prolonged, then the log-linear phase would be manifestly delayed. In the event that the terminal slope should represent k_a rather than the slowest disposition constant, precautions should be taken to allow for its change among treatments. Therefore, the application of simplified Eqs. 13, 16, and 18 demands that absorption is not continuing when the next dose is administered.

The importance of these constraints diminishes rapidly as steady state is approached. Accordingly, any given treatment suspected to be aberrant may be studied at times as close to steady state as is required for the specified level of accuracy.

Various checks may be included in the experimental design. The constancy of the terminal slope can be verified by judicious sampling during the log-linear phase throughout the study. Alternatively, urine samples may be included so that constancy in plasma clearance may be inferred through estimates of renal clearance (5). Observed changes in ω or $\bar{V}_{cl,r}$ can be incorporated into the analysis by appropriate modifications in Eqs. 14–18. The combined use of plasma and urinary data also permits the identification of data points free from the influence of absorption (4). Finally, most of the simplifying assumptions can be circumvented by pharmacokinetic modeling. This approach would entail the inclusion of an intravenous dosage and the application of Eq. 8 *et sequelae*.

In summary, an experimental strategy was devised for bioavailability estimation at quasi- or nonsteady state. The proposed method may be applied to most situations where steady-state comparisons are favored. The necessary requirements are that drug disposition obeys linear kinetics and that successive doses are administered when absorption is no longer operative.

The method seeks to optimize the obvious advantages and disadvantages of steady-state comparisons. The positive aspects of high drug concentration, limited sampling, and model independence (with minimal constraints) are retained with a concomitant reduction in study duration Experimentally, the nominal requirements consist of estimates of a mean plasma concentration over a specified dosage interval for each treatment and an estimate of the terminal half-life. Additional safeguards may be incorporated into the experimental design for verification.

APPENDIX

The plasma concentration in the central compartment was derived by Benet (6) for any linear N-compartment mammillary model with first-order absorption:

$$Cp = \frac{k_a F D}{V_1}\left[\frac{[\Pi_j(E_j - k_a)]e^{-k_a t}}{(\alpha - k_a)(\beta - k_a)\cdots(\chi - k_a)(\psi - k_a)} + \frac{[\Pi_j(E_j - \alpha)]e^{-\alpha t}}{(k_a - \alpha)(\beta - \alpha)\cdots(\psi - \alpha)} + \cdots + \frac{[\Pi_j(E_j - \psi)]e^{-\psi t}}{(k_a - \psi)(\alpha - \psi)\cdots(\chi - \psi)}\right] \quad \text{(Eq. A1)}$$

where:

- k_a = first-order absorption rate constant
- F = fraction of dose D absorbed
- V_1 = volume of distribution of the sampleable central compartment (compartment 1)
- Π_j = continuous product of terms with index j ranging from 2 to N; the term is defined as 1 when $N = 1$
- N = number of compartments
- j = running index of compartments having exit rate constant into compartment 1
- E_j = sum of exit rate constants from compartment j
- $\alpha, \beta, \ldots, \chi, \psi$ = hybrid rate constants; they are the roots of Laplace parameters, obtained by method of partial fractions such that $\alpha > \beta > \ldots > \chi > \psi$

As examples of Eq. A1, consider the one-compartment open model where $N = 1$ and $\alpha = k_e$:

$$Cp = \frac{k_a F D}{V_1}\left[\frac{e^{-k_a t}}{(k_e - k_a)} + \frac{e^{-k_e t}}{(k_a - k_e)}\right] \quad \text{(Eq. A2)}$$

For a three-compartment model where the three roots are α, β, and γ:

$$Cp = \frac{k_a F D}{V_1}\left[\frac{(E_2 - k_a)(E_3 - k_a)}{(\alpha - k_a)(\beta - k_a)(\gamma - k_a)}e^{-k_a t} + \frac{(E_2 - \alpha)(E_3 - \alpha)}{(k_a - \alpha)(\beta - \alpha)(\gamma - \alpha)}e^{-\alpha t} + \frac{(E_2 - \beta)(E_3 - \beta)}{(k_a - \beta)(\alpha - \beta)(\gamma - \beta)}e^{-\beta t} + \frac{(E_2 - \gamma)(E_3 - \gamma)}{(k_a - \gamma)(\alpha - \gamma)(\beta - \gamma)}e^{-\gamma t}\right] \quad \text{(Eq. A3)}$$

If the drug is repetitively given for i doses with dosage interval τ, the plasma levels during the ith interval become:

$$Cp^{(i)} = \frac{k_a F D}{V_1}\left[\frac{(1 - e^{-ik_a\tau})[\Pi_j(E_j - k_a)]}{(\alpha - k_a)(\beta - k_a)\ldots(\psi - k_a)(1 - e^{-k_a\tau})}e^{-k_a t'} + \frac{(1 - e^{-i\alpha\tau})[\Pi_j(E_j - \alpha)]}{(k_a - \alpha)(\beta - \alpha)\ldots(\psi - \alpha)(1 - e^{-\alpha\tau})}e^{-\alpha t'} + \cdots + \frac{(1 - e^{-i\psi\tau})[\Pi_j(E_j - \psi)]}{(k_a - \psi)(\alpha - \psi)\ldots(\chi - \psi)(1 - e^{-\psi\tau})}e^{-\psi t'}\right] \quad \text{(Eq. A4)}$$

where t' = time from the last dose. The average plasma level during that period is defined as:

$$\bar{C}p^{(i)} = \frac{1}{\tau}\int_0^\tau Cp^{(i)}\,dt' = \frac{k_a F D}{\tau V_1}[Q - P] \quad \text{(Eq. A5)}$$

where:

$$Q = \frac{[\Pi_j(E_j - k_a)]}{k_a(\alpha - k_a)\ldots(\psi - k_a)} + \frac{[\Pi_j(E_j - \alpha)]}{\alpha(k_a - \alpha)\ldots(\psi - \alpha)} + \cdots + \frac{[\Pi_j(E_j - \psi)]}{\psi(k_a - \psi)\ldots(\chi - \psi)} \quad \text{(Eq. A6)}$$

and:

$$P = \frac{[\Pi_j(E_j - k_a)]e^{-ik_a\tau}}{k_a(\alpha - k_a)\cdots(\psi - k_a)} + \frac{[\Pi_j(E_j - \alpha)]e^{-i\alpha\tau}}{\alpha(k_a - \alpha)\cdots(\psi - \alpha)} + \cdots + \frac{[\Pi_j(E_j - \psi)]e^{-i\psi\tau}}{\psi(k_a - \psi)\cdots(\chi - \psi)} \quad \text{(Eq. A7)}$$

At steady state where $i\tau \to \infty$ and $P \to 0$:

$$\bar{C}p^{(ss)} = \frac{k_a FD}{\tau V_1} Q \quad \text{(Eq. A8)}$$

By induction, the quantity Q can be proved to be identical to:

$$Q = \frac{\Pi_j(E_j)}{k_a\alpha\beta\cdots\chi\psi} \quad \text{(Eq. A9)}$$

An operational constant, V_0, is defined such that:

$$V_0 = \frac{\alpha\beta\cdots\chi\psi}{\Pi_j(E_j)}\cdot(V_1/\omega) \quad \text{(Eq. A10)}$$

where ω = terminal slope (slowest disposition constant ψ or k_a, whichever is smaller). Substituting Eqs. A9 and A10 into Eq. A8:

$$\bar{C}p^{(ss)} = \frac{FD}{\tau V_0\omega} \quad \text{(Eq. A11)}$$

Equation A10 is the general expression for the constant V_0, which has a dimension of volume. For example, in a two-compartment open model in which elimination takes place solely from the central compartment, *i.e.*, when $E_2 = k_{21}$:

$$V_0 = V_{d,\text{area}} = \frac{\alpha\beta}{k_{21}}\left(\frac{V_1}{\beta}\right) = \frac{\alpha}{k_{21}}V_1 = \frac{k_{10}}{\beta}V_1 \quad \text{(Eq. A12)}$$

Equation A11 shows that the average plasma levels at steady state are inversely proportional to the dosage interval τ and to the terminal slope ω.

If τ is chosen so that successive doses are given in the log-linear region of the plasma curve with the slope ω (*i.e.*, k_a or ψ, whichever is smaller), the right-hand side of Eq. A7 may be reduced to one single exponential term:

$$P \simeq \frac{[\Pi_j(E_j - \omega)]}{\omega(k_a - \omega)\cdots(\chi - \omega)} e^{-i\omega\tau} \quad \text{when } \omega = \psi \quad \text{(Eq. A13}a\text{)}$$

or:

$$P \simeq \frac{[\Pi_j(E_j - \omega)]}{\omega(\alpha - \omega)\cdots(\psi - \omega)} e^{-i\omega\tau} \quad \text{when } \omega = k_a \quad \text{(Eq. A13}b\text{)}$$

If, furthermore, ω is much smaller than the next hybrid rate constant and is also smaller than any composite exit rate constant, Eqs. A13*a* and A13*b* may be further reduced to their counterparts:

$$P \simeq \frac{\Pi_j(E_j)}{\omega k_a\alpha\cdots\chi} e^{-i\omega\tau} \quad \text{(Eq. A14}a\text{)}$$

or:

$$P \simeq \frac{\Pi_j(E_j)}{\omega\alpha\beta\cdots\psi} e^{-i\omega\tau} \quad \text{(Eq. A14}b\text{)}$$

By substituting Eqs. A9, A10, and A14 into Eq. A5:

$$\bar{C}p^{(i)} \simeq \frac{FD}{\tau V_0\omega}(1 - e^{-i\omega\tau}) \quad \text{(Eq. A15)}$$

Comparison of Eqs. A11 and A15 shows that:

$$\frac{\bar{C}p^{(i)}}{\bar{C}p^{(ss)}} = (1 - e^{-i\omega\tau}) \quad \text{(Eq. A16)}$$

which is identical to Eq. 10 in the text.

Equation 15 of the text was derived as follows. When l doses of formulation x is given with dosage interval τ and followed immediately by additional m doses of formulation y, the average plasma level during the $(m + l)$th period is given by:

$$\bar{C}p^{(m+l)} = \bar{C}p^x + \bar{C}p^y \quad \text{(Eq. A17)}$$

where $\bar{C}p^x$ is the contribution from formulation x and $\bar{C}p^y$ is that from formulation y. The expression for $\bar{C}p^x$ is:

$$\bar{C}p^x = \frac{1}{\tau}\int_{m\tau}^{(m+1)\tau} Cp^{(l)}\,dt' = \frac{k_a{}^x F_x D}{\tau V_1}\left[\frac{(1 - e^{-lk_a{}^x\tau})\,[\Pi_j(E_j - k_a{}^x)]}{k_a{}^x(\alpha - k_a{}^x)\cdots(x - k_a{}^x)(\psi - k_a{}^x)} e^{-mk_a{}^x\tau} + \cdots + \frac{(1 - e^{-l\psi\tau})\,[\Pi_j(E_j - \psi)]}{\psi(k_a{}^x - \psi)\cdots(\chi - \psi)} e^{-m\psi\tau}\right] \quad \text{(Eq. A18)}$$

Again, if the conditions to Eqs. A14*a* and A14*b* are satisfied, then:

$$\bar{C}p^x = \frac{k_a{}^x F_x D}{\tau V_1} Q_x(1 - e^{-l\omega\tau})e^{-m\omega\tau} = \frac{F_x D}{\tau V_0\omega}(1 - e^{-l\omega\tau})e^{-m\omega\tau} \quad \text{(Eq. A19)}$$

$$\bar{C}p^y = \frac{k_a{}^y F_y D}{\tau V_1} Q_y(1 - e^{-m\omega\tau}) = \frac{F_y D}{\tau V_0\omega}(1 - e^{-m\omega\tau}) \quad \text{(Eq. A20)}$$

Therefore:

$$\bar{C}p^{(m+l)} = \frac{D}{\tau V_0\omega}[F_x e^{-m\omega\tau}(1 - e^{-l\omega\tau}) + F_y(1 - e^{-m\omega\tau})] \quad \text{(Eq. A21)}$$

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