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Commentary

On the use of partial AUC as an early exposure metric

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1. Introduction

During the last decade great interest has been focused on the problem of assessing the rate of absorption in bioequivalence studies (Chen, 1992; Rostami-Hodjegan et al., 1994; Endrenyi and Al-Skaikh, 1995; Tothfalusi and Endrenyi, 1995; Macheras et al., 1996; Tozer et al., 1996; Endrenyi et al., 1998a,b). Traditionally, the maximum concentrations C_{max} of the two formulations have been used to evaluate absorption rate. Chen proposed in 1992 that the ratio of partial areas under the concentration (C)–time (t) curve measured until the peak $(AUC)_p$ of the reference product could be used to assess the equivalency of absorption rates (Chen, 1992). The concept of ''exposure'' originates from the work of Rostami-Hodjegan et al. (1994) who emphasized that the objective of bioequivalence testing should be the demonstration of essentially similar exposure to drug from different formulations. This argument moved the emphasis from the pharmaceutical considerations based on the assessment of absorption rates to safety and efficacy issues. In this context, Tozer et al. (1996) called for a change from the regulatory expectation of equivalent absorption rates to a requirement of equivalent systemic exposure. Accordingly, the partial area $(AUC)_p$ was re-interpreted (Tozer et al., 1996) as an early exposure metric and it was recently recommended (AAPS News, 1998; Williams, 1999) along with the classical parameters AUC (total exposure) and C_{max} (peak exposure) for bioequivalence testing. According to investigators of the US Food and Drug Administration (FDA) (AAPS News, 1998) the rational for the use of $(AUC)_p$ as an early exposure metric relies on the more accurate way of determining time of action. It is suggested (Williams, 1999) that the assessment of early exposure for immediate release dosage forms is important when a rapid onset is required or a slow input rate is needed. Also, early exposure may be used as a safeguard against dose-dumping or to assess comparability of concentration–time profiles for modified release dosage forms (Williams, 1999).

The use of AUC and C_{max} as metrics for total and peak exposure, respectively, is well documented since it parallels their extensive use in bioequivalence studies as measures of extent and rate of absorption, respectively. However, no clinical rationale has been reported for the use of $(AUC)_p$ as an early exposure metric. As a consequence it will not be long before we enter into the debate about the rationale for the use of $(AUC)_p$ in bioequivalence studies. This commentary tries to initiate this discussion. To this end, a pharmacokinetic–pharmacodynamic model was utilized and a number of simulations to explore the relationship between $(AUC)_p$ and pharmacodynamic parameters were carried out.

2. Simulations

In order to assess the utility of $(AUC)_p$ as an early exposure metric the effect compartment model introduced by Sheiner et al. (1979), was applied assuming a delay in the effect against the plasma concentration. The methodology utilized is described in the Appendix.

The plasma concentration–time curves generated from Eq. (A.3) (see Appendix) are depicted in Fig. 1. The pharmacological responses, $E_{C_{max}}$, corresponding to C_{max}, utilizing three EC_{50} values are plotted in Fig. 2 as a function of the $(AUC)_p$ values calculated from the curves of Fig. 1. As expected, the lower the value of EC_{50} the higher the effect observed at C_{max}. When flip-flop kinetics, i.e., $(k_a/k_e)<1$ is operating, an approximately linear

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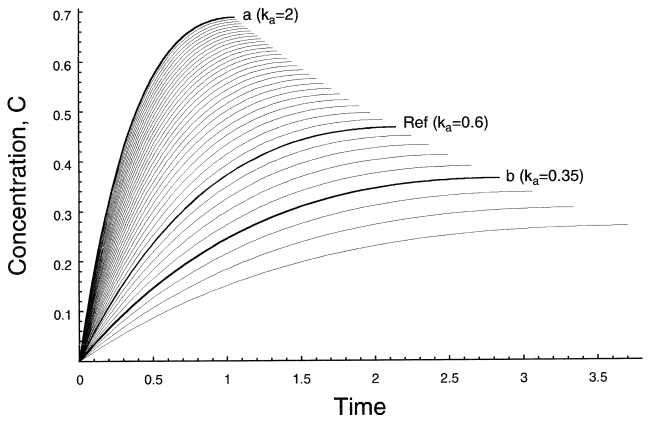

Fig. 1. Plasma concentration–time profiles up to t_{max} generated from Eq. (A.3) quoted in the Appendix, using $(FD/V)=1$, $k_e=0.355$, and values for k_a from top to bottom: 2 to 0.2 descending by 0.05.

relationship between $E_{C_{max}}$ and $(AUC)_p$ is observed (right hand side limbs of the graphs in Fig. 2). Besides, these almost linear limbs have positive slopes ranging from ~0.59 to ~1.33 from top to bottom. Although a proportionality between $E_{C_{max}}$ and $(AUC)_p$ under flip-flop kinetic conditions is a desirable feature, its deviation from the ideal behavior (dashed line in Fig. 2) is heavily dependant on the EC_{50} value. However, the issue of nonlinearity in relation to the slope of the curves being less or more than 1 is important. Slopes which are less than 1 indicate that an 80–125% limit on $(AUC)_p$ is reflected to a smaller limiting range on the effect measures, while a slope higher than 1 indicates that a limiting range of 80–125% in $(AUC)_p$ does not guarantee the same level with regard to effect measures. It is worthy to mention that non of previous studies showed slope higher than 1 for surrogate versus ideal measure (Rostami-Hodjegan et al., 1994; Elkoshi, 1999). In contrast, the parameters $E_{C_{max}}$ and $(AUC)_p$ seem to be uncorrelated under classical kinetic conditions, $(k_a/k_e)>1$, (nonlinear, concaving downwards limbs of the graphs in Fig. 2). In reality, the graphs of Fig. 2 do not correspond to a function since a function cannot associate two different $(AUC)_p$ values to one value of $E_{C_{max}}$. An example of this peculiar kinetic–dynamic relationship between $E_{C_{max}}$ and $(AUC)_p$ is presented in Fig. 3. The two effect–time profiles depicted in Fig. 3 differ considerably but exhibit identical $E_{C_{max}}$ values. Moreover, the maximum effect is elicited in both cases at time points longer than the times corresponding to C_{max}, Fig. 3, and in reality when the plasma drug concentration is in the declining phase, Figs. 1 and 3. These observations are in accord with the delay character of the pharmacokinetic–pharmacodynamic model since counterclockwise hysteresis loops are routinely obtained when the pharmacodynamic effect is plotted as a function of the plasma drug concentration. However, these results pose the question for the most appropriate, if any, cut-off time point for calculating the partial area as a measure of early drug exposure. Although this problem has been addressed in a recent study (Endrenyi et al., 1998a) this investigation considered only the statistical features in a pharmacokinetic system and did not look at consequences to pharmacodynamic exposure.

Similar behavior is observed between $t_{EC_{50}}$ the time at which the concentration in the effect compartment reaches EC_{50} and $(AUC)_p$, Fig. 4. Again, reasonable results are obtained when flip-flop kinetics is considered since an almost linear diminution of $t_{EC_{50}}$ follows the corresponding increase of $(AUC)_p$ (a roughly linear limb of the lower graph in Fig. 4). Again, the deviations from the ideal behavior (slope $=-1$, dashed line of Fig. 4) are consider-

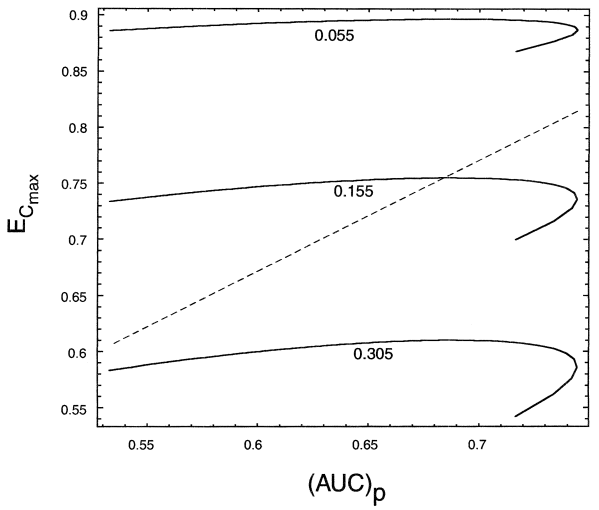

Fig. 2. The effect, $E_{C_{max}}$, evoked at C_{max} as a function of $(AUC)_p$, for various values of EC_{50} indicated. Simulations were performed using Eqs. (A.1, A.2 and A.3) (see Appendix) with $(FD/V)=1$, $k_e=0.355$, $(FDk_{iE}/V_E)=1$, $k_{E0}=0.555$ and k_a ranging from 2 to 0.2. The dashed line corresponds to the ideal (slope=1) linear relationship of the two parameters.

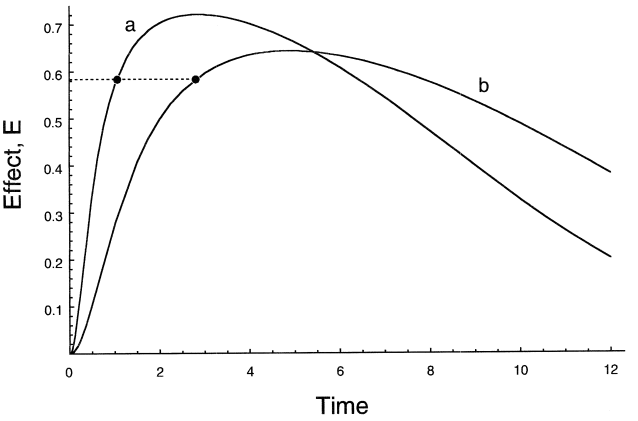

Fig. 3. The effect E as function of time for the two bold concentration–time curves ''a'' and ''b'' of Fig. 1 with different $(AUC)_p$ values, 0.532 (a) and 0.744 (b). The two E, t curves share a common $E_{C_{max}}$ value, 0.583 indicated on the ordinate. The value of EC_{50} is 0.305.

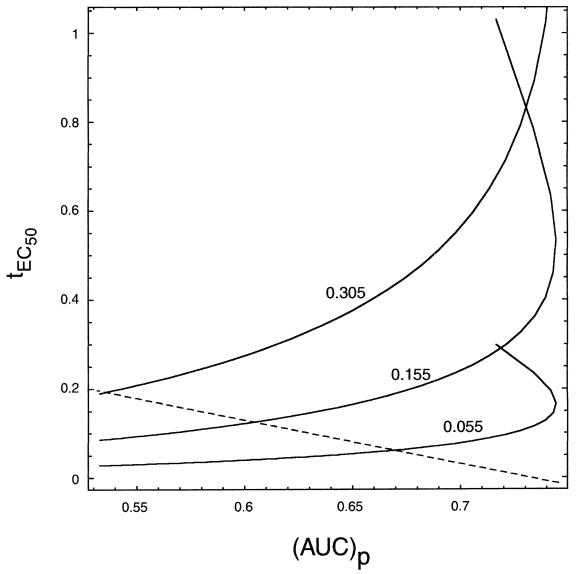

Fig. 4. The time, $t_{EC_{50}}$, at which the concentration in the effect-compartment reaches EC_{50} as a function of $(AUC)_p$ for various values of EC_{50} indicated. Simulations were performed using Eqs. (A.1, A.2 and A.3) (see Appendix) with $(FD/V)=1$, $k_e=0.355$, $(FDk_{iE}/V_E)=1$, $k_{E0}=0.555$ and k_a ranging from 2 to 0.2. The dashed line corresponds to the ideal (slope = −1) linear relationship of the two parameters.

able and EC_{50} dependant. In reality, the $(AUC)_p$ metric reflects, with a decreasing sensitivity as the values of EC_{50} increase, the onset of action if one relates it with the value of $t_{EC_{50}}$. However, this is not the case for the relationship of the parameters $t_{EC_{50}}$ and $(AUC)_p$ under classical kinetic conditions, $(k_a/k_e)>1$. $t_{EC_{50}}$ increases nonlinearly with the increase of $(AUC)_p$ (nonlinear limbs of the graphs in Fig. 4). This nonlinear relationship is inappropriate for the $(AUC)_p$ metric designed to serve as an indicator for the onset of action.

Although the aforementioned analysis reveals the relationship between the pharmacodynamic parameters $E_{C_{max}}$, $t_{EC_{50}}$and $(AUC)_p$, in a typical bioequivalence crossover study the ratio of the partial areas for the test and the reference products are used for bioequivalence assessment. Usually, $(AUC)_p$ is calculated to the earlier t_{max} or the t_{max} of the reference product for each individual (Chen, 1992; Macheras et al., 1994; Endrenyi et al., 1998a,b). A number of this comparative type of calculations were carried out for the C–t profiles of Fig. 1, assuming that the reference product corresponds to the graph denoted by ''Ref''; all other graphs were considered to represent test products and their partial areas were calculated to the earlier t_{max} or the t_{max} of ''Ref''. The corresponding relative pharmacodynamic parameters for the effect, $[E^{t_{max,earlier}}]_{T/R}$, $[E^{t_{max,Ref}}]_{T/R}$ and the time $[t_{EC_{50}}]_{T/R}$ for both cases examined, were calculated too.

The results of this set of calculations are presented in Figs. 5 and 6. Visual inspection of Fig. 5A reveals that the ratio of the partial areas calculated to the t_{max} of the

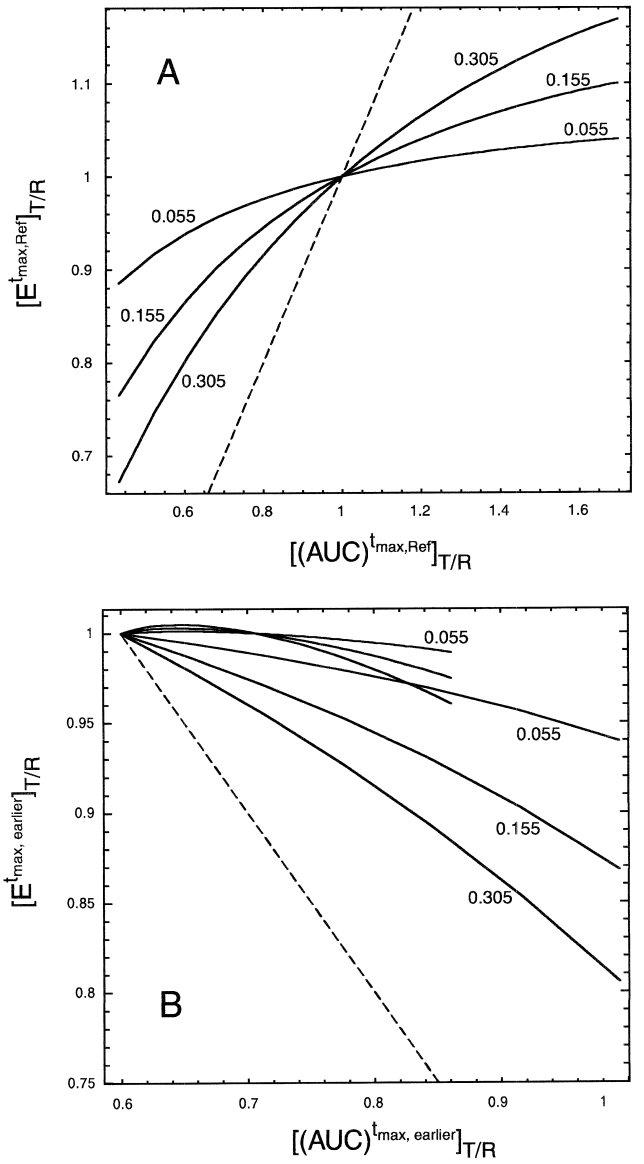

Fig. 5. The ratio of effects at the t_{max} of the reference product (designated as ''Ref'' in Fig. 1) (A) and the earlier t_{max} (B) as a function of the corresponding partial areas ratio for the values of EC_{50} indicated. Simulations were performed using Eqs. (A.1, A.2 and A.3) (see Appendix) with $(FD/V)=1$, $k_e=0.355$, $[FDk_{iE}/V_E]=1)=1$, $k_{E0}=0.555$ and k_a ranging from 2 to 0.2. The dashed line indicates the ideal (slope = 1) linear relationship of the two parameters.

reference product are not reflected linearly on the corresponding changes in the effect at the t_{max} of the reference product. This nonlinear relationship becomes more patent as the value of EC_{50} decreases, i.e., larger deviation from the ideal behavior indicated by the dashed line in Fig. 5A. A similar or even worse picture is obtained when $[E^{t_{max,earlier}}]_{T/R}$ is plotted versus the partial areas calculated up to the earlier t_{max}, Fig. 5B. By contrast, the nonlinear relationship between $[t_{EC_{50}}]_{T/R}$ and the ratio of the partial areas calculated up to t_{max} of the reference product does not depend strongly on the EC_{50} value, Fig. 6A. In

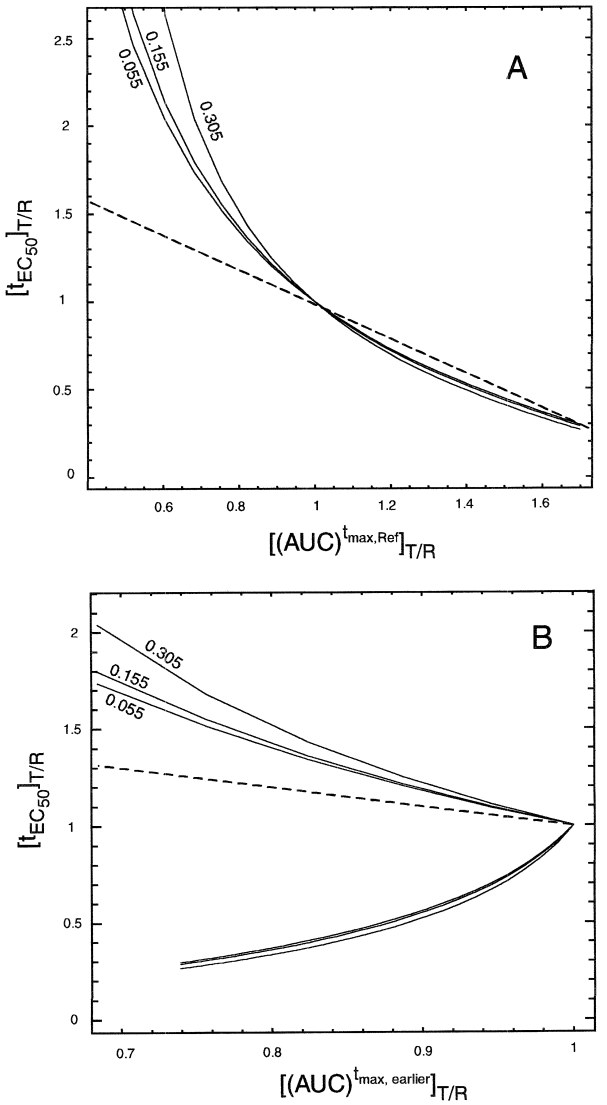

Fig. 6. The ratio $[t_{EC_{50}}]_{T/R}$ of the times at which the concentration in the effect-compartment reaches EC_{50} as a function of the corresponding partial areas ratio calculated up to the t_{max} of the reference product (designated as ''Ref'' in Fig. 1) (A) and the earlier t_{max} (B) for the values of EC_{50} indicated. Simulations were performed using Eqs. (A.1, A.2 and A.3) (see Appendix) with $(FD/V)=1$, $k_e=0.355$, $[FDk_{iE}/V_E)=1]=1$, $k_{E0}=0.555$ and k_a ranging from 2 to 0.2. The dashed line indicates the ideal (slope $=-1$) linear relationship of the two parameters.

addition, the deviation of the graphs from the ideal behavior is modest for the crucial interval 0.8–1.25 for both parameters ratios, Fig. 6A. However, the plot of $[t_{EC_{50}}]_{T/R}$ as a function of the ratio of the partial areas calculated up to the earlier t_{max} exhibits remarkable deviation from the ideal behavior, Fig. 6B. Indeed, the lower limbs of the graphs in Fig. 6B increase nonlinearly with the increase of $[(AUC)^{t_{max,earlier}}]_{T/R}$. This kind of behavior is exhibited by the test products obeying classical kinetics ($k_a/k_e>1$), Fig. 1, and is fully undesirable.

3. Conclusions

The results obtained can be explained on the basis of the pharmacokinetic–pharmacodynamic model utilized. Since this model (Sheiner et al., 1979) exhibits a delay in the effect against the plasma concentration, the changes in the pharmacodynamic parameters $E_{C_{max}}$ and $t_{EC_{50}}$ are reflected adequately on the $(AUC)_p$ metric only under flip-flop kinetic conditions. It seems likely that under these conditions the delayed onset and intensity of action as expressed in terms of $t_{EC_{50}}$ and $E_{C_{max}}$, respectively, are followed adequately by the $(AUC)_p$ metric. In contrast, the pharmacodynamic effect is not mirrored properly on the $(AUC)_p$ under classical kinetic conditions. This is due to the delay character of pharmacokinetic–pharmacodynamic model utilized in conjunction with the rapid plasma concentration changes in the early phase of plasma concentration–time profile.

The assessment of the partial area utilizing the more pragmatic scenario of comparative studies (Figs. 5 and 6) leads to conclusions which are dependant on the partial area utilized, the pharmacodynamic parameter considered as well as the value of EC_{50}. Fig. 6A demonstrates that the relative value of $t_{EC_{50}}$ mirrors adequately the relative partial area calculated up to the t_{max} of the reference product for the crucial interval 0.8–1.25 of the parameters ratio in a wide range of EC_{50} values examined. Thus, the relative partial area calculated up to the t_{max} of the reference product can be considered as an acceptable measure of early drug exposure since $t_{EC_{50}}$ can be associated with the onset of action. When the assessment of the partial area ratio as an early exposure metric is based on the relative effect of the two products, the results are not at all encouraging, Fig. 5. This conclusion applies to both types of partial areas examined, i.e., up to the t_{max} of the reference or up to the earlier t_{max}. In all cases, remarkably nonlinear relationships, highly dependent on the EC_{50} value were found, Fig. 5. The discrepancy of the conclusions derived from Figs. 5 and 6 originates from the degree of the nonlinearity of the mathematical expressions relating the pharmacodynamic parameters $t_{EC_{50}}$ and $E_{C_{max}}$ with $(AUC)_p$. It seems likely that the relationship between $t_{EC_{50}}$ and $(AUC)_p$ is much less nonlinear than the corresponding between $E_{C_{max}}$ and $(AUC)_p$.

Although the early exposure concept is both correct and attractive, the complexity, nonlinearity and diversity of the pharmacodynamic phenomena imply that the use of a global, unique metric for assessing early drug exposure should be examined with caution. It is advisable to consider each drug individually and the appropriateness of the utilized metric(s) be based on a large number of pharmacokinetic–pharmacodynamic data and well established relationships between the proposed early exposure metric(s) and the onset and/or intensity of action. It is

hoped that the present commentary will facilitate such a quest.

Appendix

The pharmacological effect (E) was related to the concentration of the effect-compartment (C_e) by Eq. (A.1):

$$E = \frac{E_{max} C_e}{EC_{50} + C_e} \quad (A.1)$$

where E_{max} and EC_{50} denote the maximum effect and concentration where the half-maximal effect is evoked, respectively. For simplicity, in all simulations E_{max} was set to unity. C_e was calculated (Yu and Tse, 1994) with a conventional one-compartment model with first-order input as follows:

$$C_e = \frac{FDk_{iE}}{V_E} \cdot k_a \cdot \frac{(k_e - k_{E0})e^{-k_a t} + (k_{E0} - k_a)e^{-k_e t} + (k_a - k_e)e^{-k_{E0} t}}{(k_a - k_e)(k_e - k_{E0})(k_a - k_{E0})} \quad (A.2)$$

where k_{iE} is the input rate constant from the plasma to the effect compartment, k_{E0} indicates the elimination rate constant from the effect compartment, F is the bioavailable fraction of dose D, V_E is the apparent volume of distribution of the effect compartment, and k_e, k_a are the elimination and the absorption rate constants of the plasma compartment, respectively. In all simulations FDk_{iE}/V_E was set to unity. The time courses of plasma drug concentrations up to C_{max} were generated using Eq. (A.3):

$$C = \frac{FDk_a}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) \quad (A.3)$$

where V is the apparent volume of distribution of the plasma compartment. To mimic either immediate or slow release formulations, various choices of k_a/k_e values were utilized.

Values of $(AUC)_p$ were obtained by integrating Eq. (A.3). Values for $t_{EC_{50}}$ were obtained by numerical solution of Eqs. (A.1 and A.2).

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