Nonlinear dynamics in Clinical Pharmacology: the paradigm of cortisol secretion and suppression

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Keywords: chaos, circadian rhythm, corticosteroids, cortisol, hormones, pulsatility

Introduction

The proper use of a medicinal agent is based on its pharmacokinetic (PK) and pharmacodynamic (PD) characteristics. However, PK and PD parameters are subject to considerable intra- and inter-subject variability. Careful analyses during the last decade revealed that PDs is definitely more variable than PKs [1]. It is generally believed that the determinants of PD variability are unknown since the factors affecting concentration-response relationships are numerous [2]. This idea relies on the classical, stochastic view of randomness. However, over the last two decades the science of nonlinear dynamics has shown that complex-random looking behaviour can be generated by deterministic systems [3]. Although only classical randomness is clearly involved in most PD studies, e.g. chemotherapy, a considerable part of the variability in some PD studies, e.g. cardiovascular, CNS, hormonal, may originate from a nonlinear system with even a few degrees of freedom [4]. This argument relies on the principles of nonlinear dynamics [5] as applied to complex biological systems [6–8]. In addition, the ligand–receptor interaction exhibits nonlinear dynamic behaviour when feedback mechanisms are involved [9, 10].

One of the physiological processes where nonlinear dynamics is believed to play an important role is the secretion of hormones. The erratic behaviour of hormone secretion originates from the complex dynamics involved. Numerous applications of nonlinear dynamics to the secretion of hormones have been published [11–17]. In this context, various methods for the analysis of the chaotic nature of the pulsatile secretion of hormones have been reported [18–20].

In the following sections we present a brief summary of the basic properties of a dynamical system and an example of a nonlinear dynamical model which describes erratic plasma cortisol concentrations, as well as the effect of corticosteroids upon them. The latter gives an opportunity to discuss the concept of variability in PK and PD studies from a dynamical systems' perspective.

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Received 17 July 2001, accepted 18 February 2002.

The essential properties of a dynamical system

A dynamical system is a deterministic mathematical system that can be represented by a set of differential equations of the form:

$$dx/dt = f(x, t).$$

The number of variables needed to describe the state of the system, which is the number of initial conditions needed to determine its time evolution (trajectory) in a unique way, is the dimension of the system. The set of these variables form a mathematical space called phase space [8]. However, there are dynamical systems that have infinite dimension. Such systems are usually described by differential equations with partial derivatives or time-delay differential equations and can be considered as a set of infinite in number ordinary differential equations [5]. The phase space is a valuable tool in dynamical systems analysis since it is easier to analyse the properties of the dynamical system by determining the topological properties of the trajectories rather than analysing the time series of the values of the variables directly. The dynamical study of systems of unknown dimension, like real-world data, or systems of infinite dimension, like systems described by partial differential equations, is usually based on the construction of a pseudo-phase space [5, 8] using as coordinates the values of a variable at different time points.

The solutions of most dynamical systems, in the long run, are confined to a limited part of the phase space which is called the attractor [5], i.e. the set of points in the phase space to which the trajectories are attracted. Every trajectory that starts outside the attractor tends to move towards it as time passes. An attractor is usually an object of lower dimension than the entire phase space (a point, a circle, a torus, etc.). For example, a multi-dimensional phase space may have a point attractor

(dimension 0), which means that all trajectories tend to concentrate in a specific point in the phase space. Even the solutions of systems with infinite dimension may lie on attractors of low dimension which emerge by the use of a pseudo-phase space.

Some dynamical systems with three or more differential equations which include nonlinear terms, may exhibit chaotic behaviour [3], defined as trajectories that follow complicated non-periodic patterns that resemble randomness. This behaviour only occurs for a specific range of the parameter values of the system. Hence, these systems exhibit qualitatively different behaviour for a change (sometimes even slight) in the parameter values.

The main characteristic of chaotic dynamics is the sensitivity of the evolution of the system from initial conditions. This means that a slight change in the initial conditions produces a completely different trajectory. The deviation of two initially neighbouring trajectories increases exponentially with time, i.e. proportional to $\exp(\lambda t)$. λ is called the Lyapunov exponent [7] and is a measure of chaos. Thus, if a system has at least one positive Lyapunov exponent, it is considered chaotic. This characteristic implies nonpredictability of the time evolution of the system in the long run, due to our inability to know the initial conditions with infinite accuracy.

Like other dynamical systems, chaotic systems have attractors too. Again, these attractors may be of lower dimensionality than the entire phase space. However, this dimension is not always an integer. It may be a fractal dimension [5] which defines an attractor with infinite detail but confined in a finite space. This kind of attractor is called a strange attractor and the integer dimension of the entire phase space in which the attractor lives is called the embedding dimension [5] of the attractor.

Cortisol secretion

The hypothalamic-pituitary-adrenal axis (HPA) is one of the most studied hormonal systems. Most attempts to model blood cortisol concentrations in PK/PD studies are purely phenomenological and focus on describing the circadian rhythm using periodic mathematical functions. This ignores the pulsatility of cortisol secretion [21], thus producing smooth periodic curves [22–24]. However, the available experimental data are not at all smooth and there is strong evidence that plasma cortisol secretion is characterized by pulsatility and irregularity apart from diurnal variation [21, 25–28]. In a recent study [29] the irregular features of cortisol blood concentrations were ascribed to classical randomness and described through the use of stochastic differential equations.

The primary stimulus for cortisol secretion from the anterior pituitary is adrenocorticotropic hormone (ACTH), the secretion of which is mainly stimulated by hypothalamic corticotropin-releasing hormone (CRH). Cortisol causes feedback inhibition of ACTH both by acting directly on the pituitary and by decreasing CRH secretion. However, the real picture of the feedback mechanism is much more complex if one takes into account the diurnal rhythm of cortisol secretion and, in addition, the interactions of the hypothalamic-pituitary-adrenal axis with the CNS and stress systems [27, 30, 31], (Figure 1).

A dynamical system for cortisol kinetics

Although the detailed features of the interactions involved in cortisol secretion are still unknown, some observations indicate that the irregular behaviour of cortisol concentrations originates from the underlying dynamics of the HPA axis system. Indeed, Ilias *et al.* [32] using time series analysis, have shown that the reconstructed phase space [5] of cortisol concentrations in healthy subjects has an attractor of fractal dimension $D_0 = 2.65 \pm 0.03$. This value indicates that at least three variables control cortisol secretion [3]. A nonlinear model of cortisol secretion with three variables, which takes into account the simultaneous changes of ACTH and CRH has been proposed [33].

These observations prompted us to model cortisol plasma concentrations relying on the well established erratic secretion rate [21] and the circadian rhythm, while other factors controlling cortisol secretion are also considered but not expressed explicitly (Figure 1). In the model presented here the features of circadian rhythm and its complex nonlinear behaviour are integrated to give realistic cortisol concentration profiles.

Cortisol concentration is described by a nonlinear time-delay differential equation [34, 35] with two terms, namely, a secretion rate term which adheres to the negative feedback mechanism [36, 37] and drives the pulsatile secretion, and a first order output term:

$$\frac{dC}{dt} = k_1 \frac{a^n C_d}{a^n + C_d^n} - k_2 C \qquad (1)$$

where C is the cortisol concentration, C_d is the value of C at time $t - T$, n is an exponent, k_1 and k_2 are the input and output rate constants, respectively. Since the main interest of this work is related to the secretion of cortisol, its complex disposition characteristics are modelled with a simple first-order rate constant, k_2. The circadian rhythm of cortisol secretion is implemented

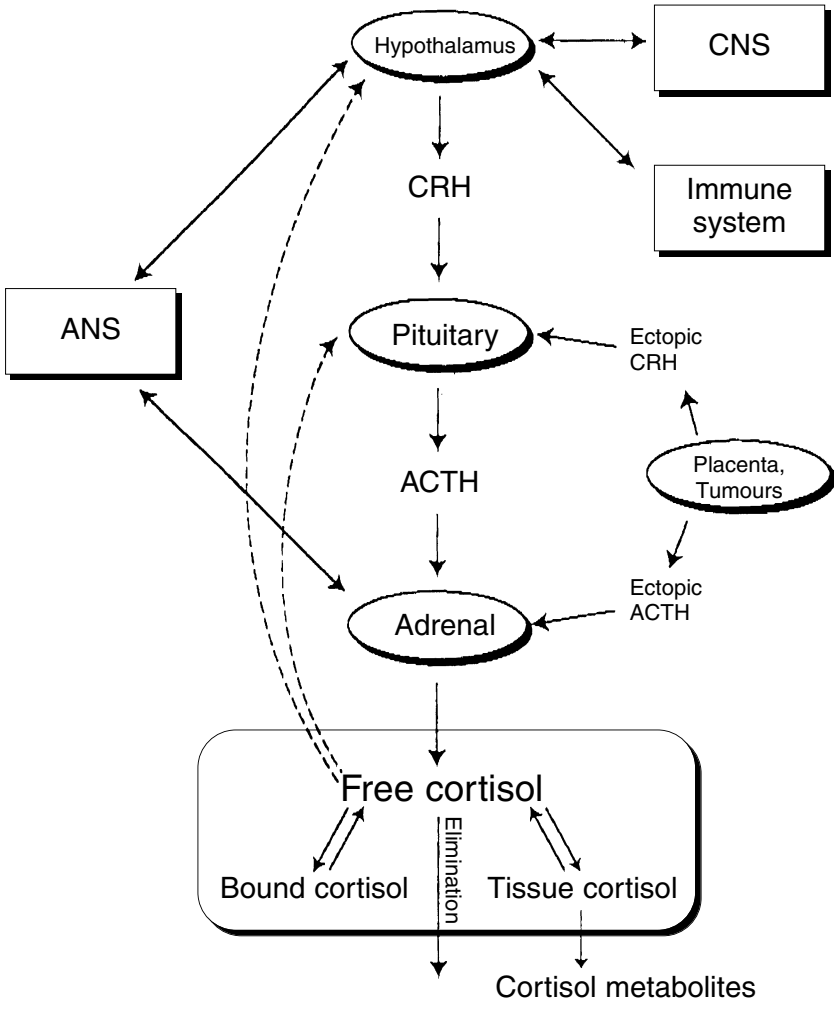


Figure 1 A schematic representation of the hypothalamic-pituitary-adrenal axis (HPA), together with other organs and systems that interplay in the secretion of cortisol. Solid arrows indicate stimulation, production or reaction and dashed arrows inhibition, while double arrows indicate more complicated bi-directional interaction. At the bottom of the graph the various components of cortisol disposition are indicated. Free cortisol, which participates in the feedback mechanism, is also in equilibrium with the cortisol species bound to corticosteroid bound globulin and tissue cortisol. In experimental studies, the measured blood cortisol levels are the sum of free and bound cortisol. Key: ANS (autonomic nervous system), CNS (central nervous system).

phenomenologically by considering the parameter of the model a as a simple cosine function of the 24 h period:

$$a = A \cdot \cos\left[(t-f)\frac{2\pi}{1440}\right] + B \qquad (2)$$

where A and B are constants with concentration units, f is a constant with time units and t is time in min. Similar approaches relying on simple periodic functions were used by Rohatagi *et al.* [22] to describe the secretion rate of cortisol.

Our dynamical system consists of equations 1 and 2. The physical meaning of the time delay in equation 1 is that the cortisol concentration, C, affects other physiological parameters of the systems depicted in Figure 1 (not present in equation 1), which in turn affect, via the feedback mechanism, cortisol concentration and, thus, cortisol controls its own secretion [23]. This cycle is postulated to last for time T, and that is how the concentration C_d at time $t-T$ arises. The simulated profile generated by equations 1–2 is shown in Figure 2, and exhibits the circadian rhythm, as well as the pulsatile nature of the cortisol secretion system. Since equation 1 has an infinite number of degrees of freedom [38], we constructed a pseudo-phase space [5, 8] for the system of equations 1 and 2 using the model variables $C(t)$, $C(t-T/2)$, $C(t-T)$, (Figure 3). The use of three dimensions is in accordance with the embedding dimension that Ilias *et al.* [32] have found. The attractor of our system shown in Figure 3 is quite complicated geometrically, i.e. it is a strange attractor.

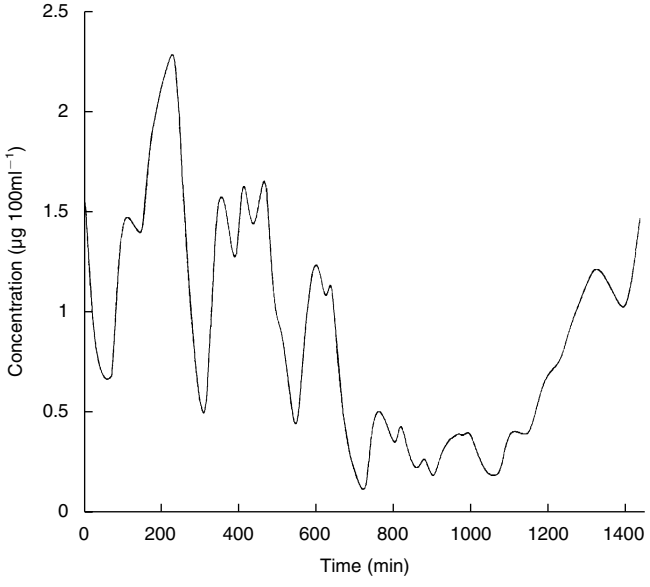


Figure 2 A 24 h simulated profile generated by the model of equations 1 and 2. Model parameters take the values $k_1 = 0.0666$ min^{-1}, $k_2 = 0.0333$ min^{-1}, $C(0) = 1.7$ μg 100 ml^{-1}, $n = 10$, $A = 0.7$ μg 100 ml^{-1}, $B = 1$ μg 100 ml^{-1}, $f = 250$ min and $T = 70$ min. Time starts from 08.00 h. The value assigned to T corresponds to about one cortisol secretion burst per hour in accordance with experimental observations [21]. The simulations were performed by a numerical solution of equations 1 and 2, using the Fortran subroutine RETARD [38].

As we have already mentioned, one of the most important features of nonlinear dynamics is their sensitivity to initial conditions. A measure to verify the chaotic nature of a dynamical system is the Lyapunov exponent [5], which quantifies the sensitive dependence from initial conditions. In the present model we found [39] the largest Lyapunov exponent to have a positive value of around 0.00011 min^{-1}, or equivalently 0.0064 h^{-1}, which is a clear indication for chaotic behaviour.

A dynamical consideration of the burst-type rate of cortisol secretion

If chaotic dynamics are present, the experimental errors associated with the pulsatility of cortisol secretion do not originate exclusively from classical randomness. Thus, the measures of central tendency used to describe or treat experimental data are questionable, since averaging is inappropriate and masks important information in chaotic systems [40]. This observation applies to the reported values of the daily cortisol production rate [26, 41] and the rationale of averaging the profiles of several subjects. In the same vein, all models mimicking only the circadian rhythm of cortisol secretion using periodic functions of time [22–24], ignore the fundamental feature of cortisol secretion dynamics, i.e. the burst-type rate of secretion, which is driven by feedback mechanisms.

The pulsatility of cortisol secretion is best depicted in the secretion rate. Owing to the erratic character of cortisol secretion, the instantaneous secretion rate should be reported, if possible, instead of the average rate in an extended period [26]. The cortisol secretion rate profile, simulated by equations 1–2 is shown in Figure 4, and shows characteristic resemblance with equivalent plots generated from deconvoluted experimental data, even with a very dense sampling design (see for example Figure 1b, c in [21]).

The pulsatile nature of cortisol secretion in conjunction with the sampling interval are crucial for the visual appearance of experimental data. This is shown in Figure 5 where a usual blood sampling interval of 30 min is used for both the experimental data from three individuals (Figure 5a, b and c) and the simulated data (Figure 5d). Data generated from the model described by equations 1–2 look visually similar to the experimental data (Figure 4). Needless to say the variation in the sampling design has no impact on the shape of the profile as far as classical models are concerned.

Variability and long time prediction of cortisol levels: a dynamical perspective

The model under study here offers an opportunity to refer to some implications of the presence of nonlinear dynamics. Apart from the jagged cortisol concentration profile, elements such as the sensitive dependence from the initial conditions (expressed by the positive Lyapunov exponent), as well as the parameters of the system, play an important role and may explain the inter- and intra-subject variability observed in the secretion of cortisol. These implications, together with other features absent from classical models, are demonstrated in Figure 6. Thus, a change in the initial conditions or the parameter values of equations 1 and 2 may be depicted in a relatively large change of the final profile (Figure 6a and b). Also, the profiles corresponding to two successive days (Figure 6c), or two different sampling designs (Figure 6d) may differ markedly, even though precisely the same set of parameter values is used. Overall, our analysis based on nonlinear dynamics offers an alternative explanation for the fluctuation of cortisol concentrations. However, the most important implication of the presence of nonlinear dynamics in cortisol secretion processes is the limitation for long-term prediction which makes practical application of the classical models questionable.

Cortisol suppression by corticosteroids

The model presented here allows the consideration of external corticosteroid administration as a perturbation of the cortisol secretion system. Corticosteroids cause a temporary diminution of plasma cortisol concentrations [22].

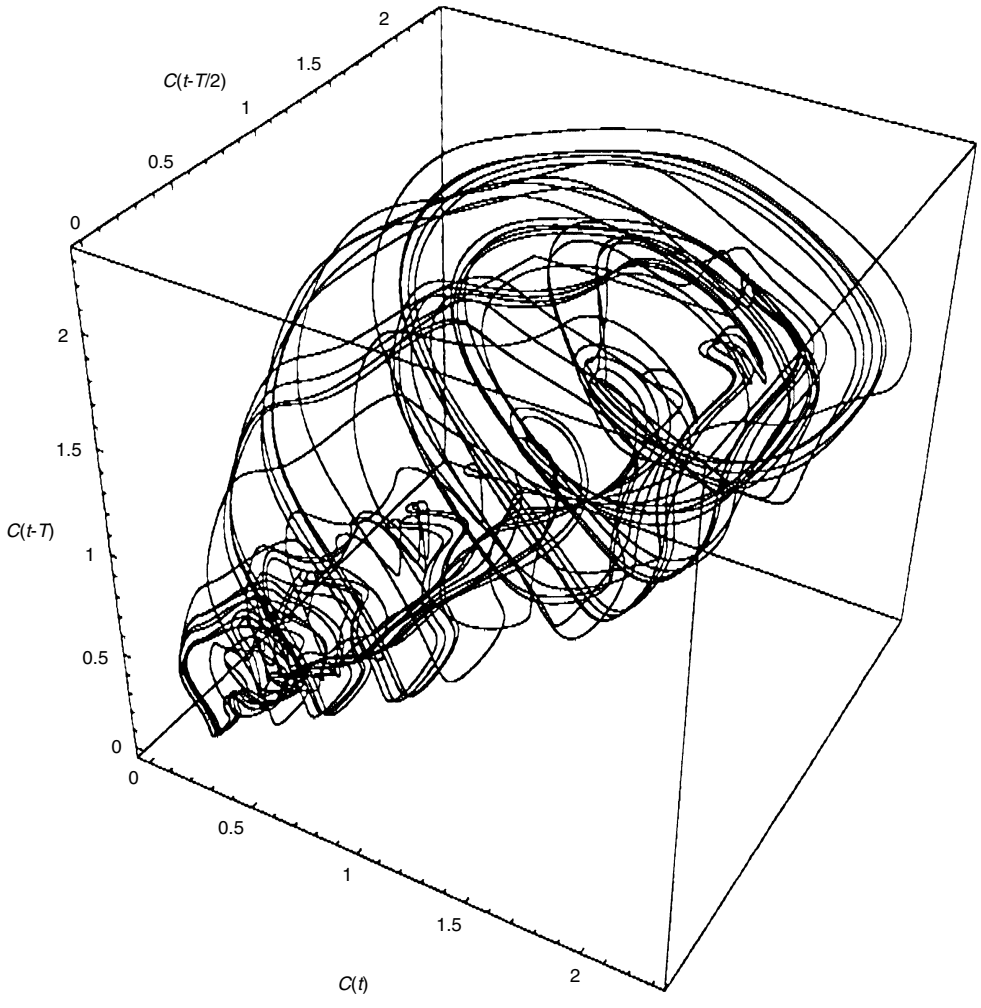
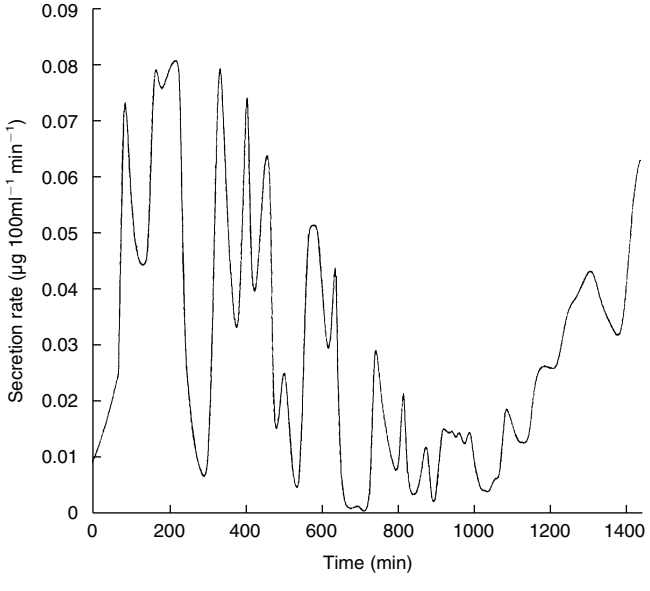


Figure 3 A pseudo-phase space for the model of equations 1 and 2 using the variables $C(t)$, $C(t-T/2)$ and $C(t-T)$ expressed in μg 100 ml^{-1}. The real phase space is of infinite dimension, however, trajectories may be considered to lie in a low dimensional space (attractor). The model parameters take the same values as in Figure 2 and time runs for 10 days.



Assuming that the drug follows one-compartment model disposition with first-order input and output, the effect-site [42] concentration is described by equation 3 [43]:

$$C_{\mathrm{E}} = \frac{F \cdot D}{V} \cdot \frac{k_{\mathrm{a}} \cdot k_{\mathrm{E0}}}{k_{\mathrm{a}} - k_{\mathrm{e}}} \cdot \left[\frac{e^{-k_{\mathrm{E0}} \cdot t} - e^{-k_{\mathrm{e}} \cdot t}}{k_{\mathrm{e}} - k_{\mathrm{E0}}} - \frac{e^{-k_{\mathrm{E0}} \cdot t} - e^{-k_{\mathrm{a}} \cdot t}}{k_{\mathrm{a}} - k_{\mathrm{E0}}} \right] \quad (3)$$

where F is the bioavailable fraction of dose D, V is the volume of distribution of the pharmacokinetic compartment, k_{a}, k_{e} are the input and elimination

Figure 4 The simulated cortisol secretion rate profile is shown; it exhibits characteristic resemblance with equivalent plots derived from experimental data (see for example Figure 1b, c in [21]). The model parameters take the same values as in Figure 2, and time starts from 08.00 h.

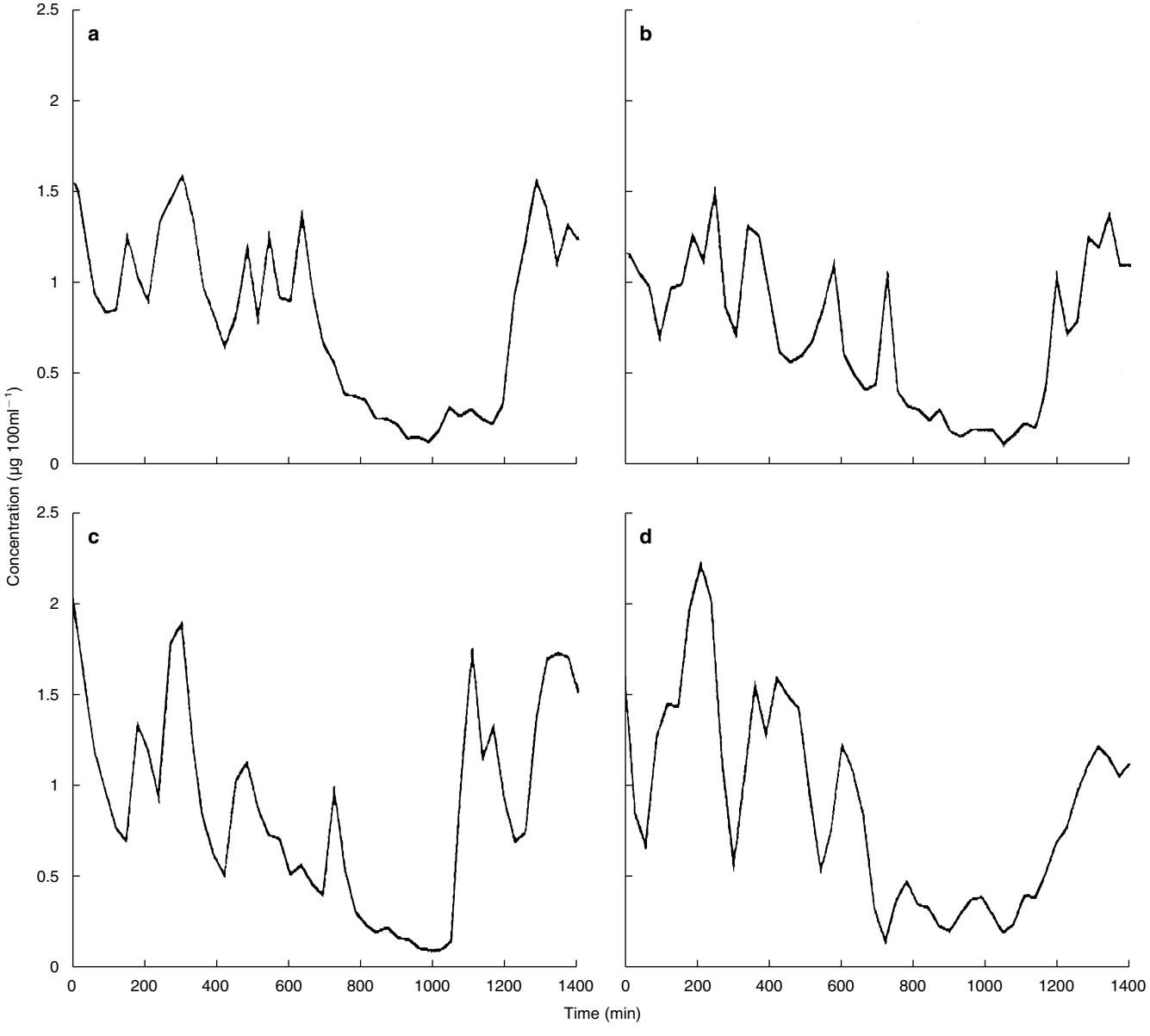


Figure 5 Plots a, b and c show 24 h endogenous cortisol profiles obtained from three young, male individuals [28]. Plot d shows data generated by equations 1 and 2 where model parameters take the same values as in Figure 2, utilizing a 30 min sampling interval. Time starts from 08.00 h. The simulated data (d) look visually similar with the experimental data (a, b, c).

first order rate constants, respectively, and k_{E0} is the elimination rate constant from the effect compartment.

The effect-site concentration of the corticosteroids can be considered to affect one or more parameters of the model described by equation 1. This must be implemented such that the presence of C_E suppresses the cortisol secretion in accordance with the experimental data. The parameter α of the model, which describes the circadian rhythm was considered to include the effect of corticosteroid administration following a receptor based diminution:

$$a' = a\left[1 - \frac{C_E}{C_{E50} + C_E}\right] \qquad (4)$$

where C_{E50} is a coefficient that expresses the concentration of the drug when $a' = a/2$. In this simple way realistic cortisol blood concentrations, following exogenous corticosteroid drug administration, can be obtained as exemplified by the case of fluticasone propionate (Figure 7) [23]. The simulated profiles correspond to two 'individuals' where only the initial value of C differs producing, however, significantly different profiles. In parallel, the sensitive dependence of the detailed final profile from the exact values of the concentration C_E should be emphasized, since C_E directly affects one of the parameters of the chaotic oscillator (equation 4). Finally, the large inter- and intra-subject variability

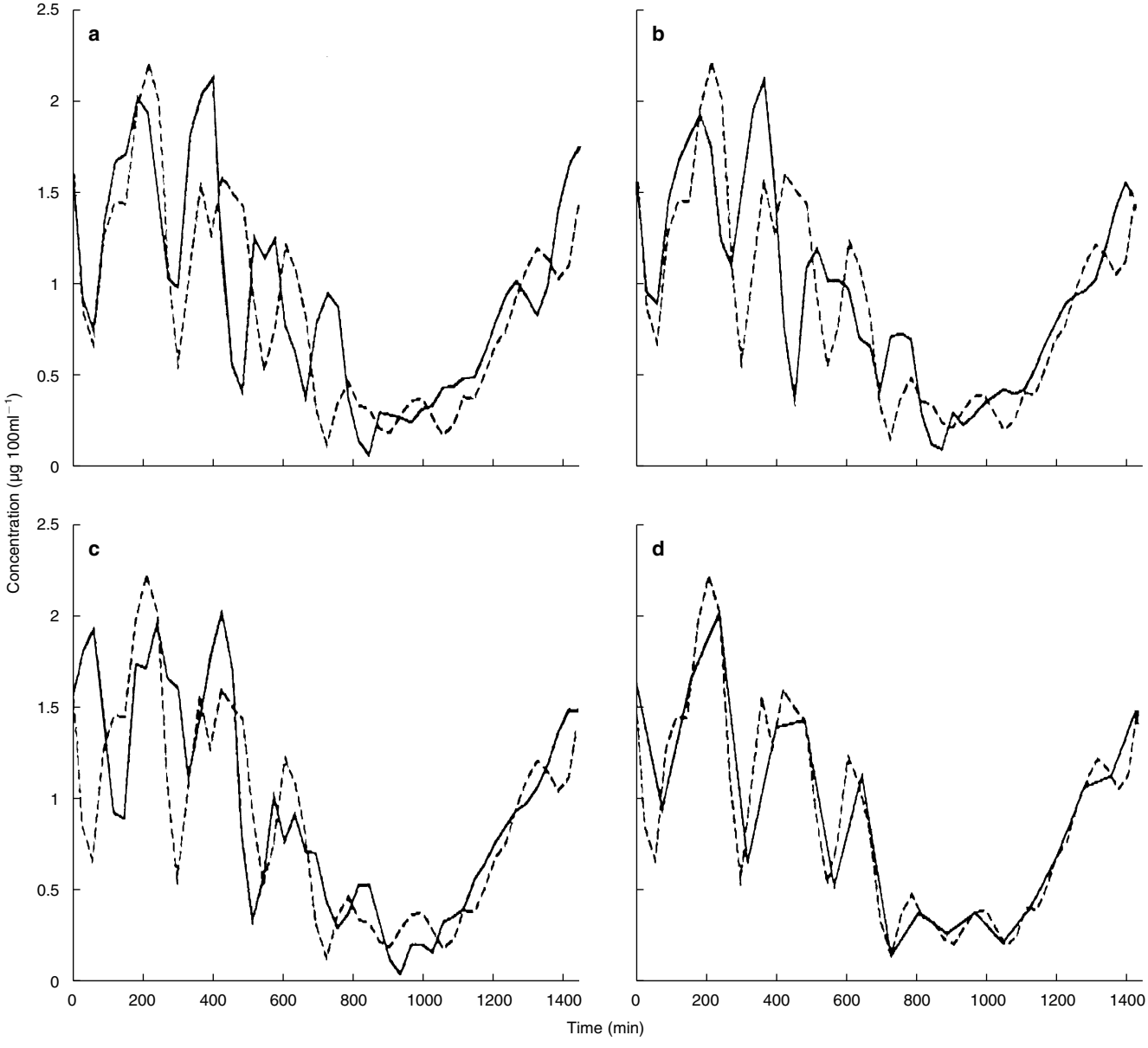


Figure 6 The chaotic nature of the model has several important implications. In all plots the dashed line is generated from equations 1 and 2 using the parameter values quoted in the legend of Figure 2 while the sampling interval is fixed to 30 min. The solid lines correspond to the same set of parameter values applying a change only in one of them. This change, however, is enough to produce significant visual change in the profile: (a) k_2 is set to 0.03 min^{-1}; (b) $C(0)$ is set to 1.6 μg 100 ml^{-1}; (c) the second's day profile is compared with the first's day profile; (d) sampling is performed every 80 min instead of 30 min. The dashed and solid lines of plots c and d have identical values for the model parameters. Time starts from 08.00 h.

observed in studies investigating the effect of fluticasone propionate on cortisol concentrations [44] can be explained by the erratic behaviour of the system of equations 1–4.

Conclusions

Experimental evidence indicates that fluctuations in cortisol secretion are not produced by random processes. In the present commentary, the chaotic nature of these fluctuations is described by a simple deterministic model based on the physiological mechanisms involved. This approach allows a straightforward derivation of a pharmacodynamic model describing the effect of corticosteroids on cortisol blood concentrations. The important result of this study is the opportunity that it offers to discuss the implications of the presence of nonlinear dynamics in processes such as the secretion of cortisol. Based on the aforementioned discussion, it is evident that the concepts of deterministic nonlinear dynamics should be adopted in pharmacodynamic modelling when supported by experimental and physiologic data. This is valid not only for the

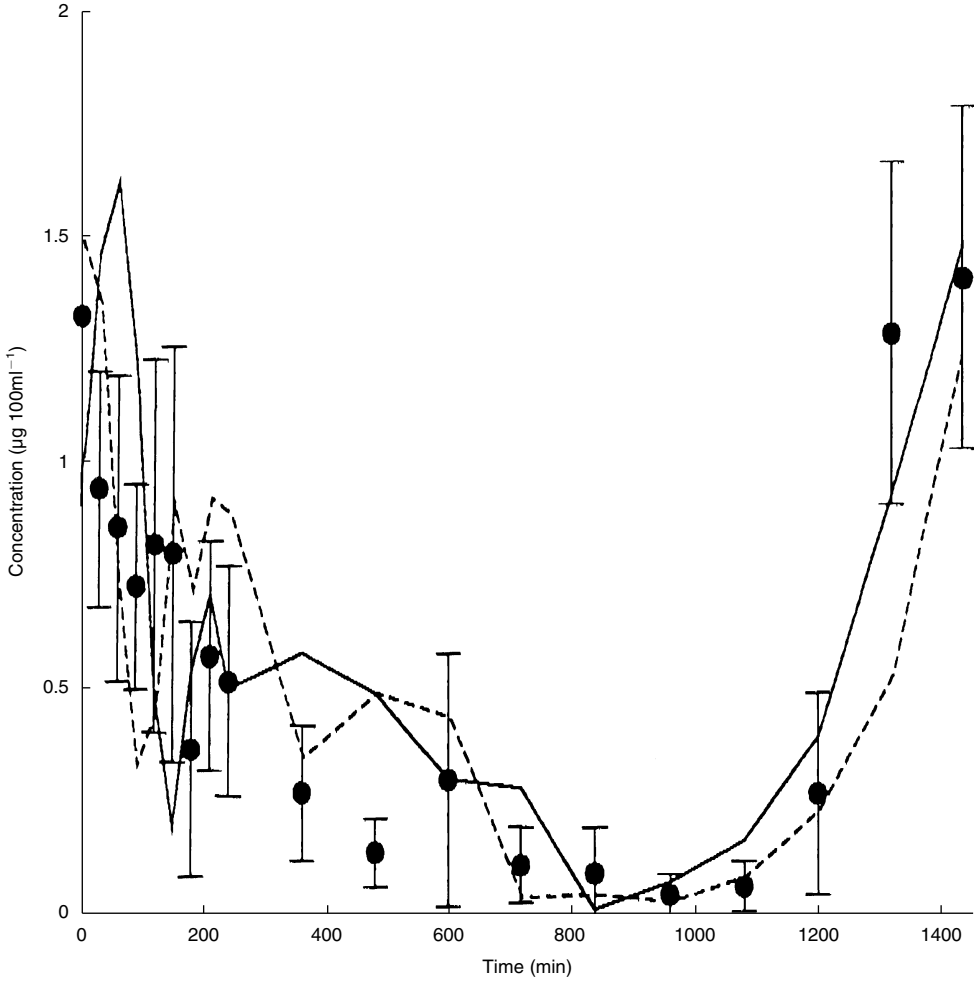


Figure 7 Diminution of cortisol blood concentrations in the presence of fluticasone propionate. Circles represent averaged experimental data of four volunteers after the administration of 1 mg of inhaled drug [23], while the solid and dashed lines, generated by equations 1–4, represent simulated data for two 'individuals' with different initial conditions. Parameter values: $k_1 = 0.0666$ min^{-1}, $k_2 = 0.0333$ min^{-1}, $n = 10$, $A = 0.9$ μg 100 ml^{-1}, $B = 1$ μg 100 ml^{-1}, $f = 200$ min, $T = 70$ min, $V = 22.2$ l, $k_a = 0.14$ min^{-1}, $k_e = 0.002$ min^{-1}, $k_{E0} = 0.005$ min^{-1}, $F \times D = 1000$ μg, $C_{E50} = 2$ μg 100 ml^{-1} and $C(0) = 0.9$ μg 100 ml^{-1} (solid), $C(0) = 1.5$ μg 100 ml^{-1} (dashed). Time starts from 08.00 h. The values of the model parameters were selected in order to generate qualitatively similar profiles to the experimental data and were not optimized since fitting is not well established for chaotic systems.

sake of more detailed study, but mainly because nonlinear dynamics suggest a whole new rationale fundamentally different from the classic approach. Moreover, the clinical pharmacologist should be aware of the limitations of chaotic models for long-term prediction, which is contrary to the routine use of classical models.

We wish to thank Dr A. Gravanis, Department of Medicine, University of Crete, for helpful discussions. We would also like to thank Dr A. Vgontzas, Department of Psychiatry, Pennsylvania State University for providing the individual cortisol data.

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