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Predicting the concentration level of an anti-cancer drug during treatment of a living organism

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Summary For many drugs used in chemotherapy the difference between the therapeutic concentration and the toxic concentration is small. During treatment of a living organism from cancer by using chemotherapy, it is therefore important to foresee the therapeutic concentration in the organism as a function of the injected therapeutic drug dose. This article provides a mathematical dynamic description of the interaction between the organism and the drug, and analyses the dynamics by using ordinary differential equations. The model is tested in a clinical situation where digitoxin is used as the therapeutic drug. The agreement with this experiment is good.

INTRODUCTION

A considerable amount of experiments have been carried out to test the growth and proliferation of malignant and benign cells. For several of the drugs used in chemotherapy the difference between the therapeutic concentration and the toxic concentration is very small, and the ability to foresee the concentration level in the organism is then very important. Lacking is to our knowledge the differential equations that describe such a type of problem. By using differential equations we are able to foresee the dynamics of the concentration much better than by using polynomial extrapolations.

Inspired by the results presented on the anti-cancer effects of cardiac glycosides (1), Haux et al. (2) examined the effect of digitoxin, and more specifically the effect of digitoxin on different malignant cell lines. They showed that digitoxin inhibited the proliferation of cells for most of the malignant cell lines by increasing the number of apoptotic and necrotic cells. However the normal cell lines were not affected by the digitoxin treatment.

Inspired by the results from (2) and others this article builds a mathematical model based on the theory of differential equations in order to understand the dynamics of the concentration in an organism in a more fundamental way. The model is tested against empirical results. For a given dose the model's intrinsic predictive power is used to run simulations 20 days into the future. The model can be used to pinpoint the critical drug dose where the drug level is near the toxic level.

The following section provides the theoretical model. The third section compares the model with results from in vivio experiment and the last section concludes.

THE DETERMINISTIC THEORETICAL MODEL

Let $m(t)$ be the expected mass of a specific drug in the organism and outside the digestive track (stomach and intestine; stomach for short), at time t. This section applies expected values for all variables and we suppress

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the word expectation hereafter. We define the drug concentration in the organism by

$$c(t) \stackrel{\text{def}}{=} m(t)/V, \qquad [2.1]$$

where V is the drug space (volume) in the organism. It is well known that this concentration of a drug in the organism determines the death rate and the mitosis rate for malignant cells.

Let $ms(t)$ be the mass of the drug in the stomach at time t, and define the following concentration

$$cs(t) \stackrel{\text{def}}{=} ms(t)/V. \qquad [2.2]$$

Let $qi(t)$ be the mass which is injected into the stomach per unit time, and let $qu(t)$ be the mass leaving the stomach and moving into the drug volume V per unit time. Assuming that during a time interval Δt the drug is mainly digested we have

$$\Delta ms(t) \stackrel{\text{mod}}{=} qi(t)\Delta t - qu(t)\Delta t. \qquad [2.3]$$

where 'mod' means a testable model assumption. When Δt approaches zero we get after dividing with V the differential equation

$$\dot{c}s(t) = (qi(t) - qu(t))/V, \qquad [2.4]$$

$qi(t)$ is an external given function and describes how the organism is fed by drugs.

A model for $qu(t)$ is given by

$$qu(t) \stackrel{\text{mod}}{=} a_1 ms(t), \; a_1 = \text{constant}. \qquad [2.5]$$

The differential equation for the concentration in the stomach follows from [2.4] and [2.5] as

$$\dot{c}s(t) = qi(t)/V - a_1 cs(t). \qquad [2.6]$$

The increase of mass in the drug space V during a time interval Δt is

$$\Delta m(t) \stackrel{\text{mod}}{=} qu(t)\Delta t - qe(t)\Delta t, \qquad [2.7]$$

where $qe(t)\,\Delta t$ is the mass of drugs leaving the organism during a time interval Δt. We hypothesize that this amount is dependent of the mass in the volume V. A simple model is

$$\begin{aligned} qe(t) &\stackrel{\text{mod}}{=} qemax(1 - \text{Exp}[-a_2 m(t)/qemax]), \\ a_2 &= \text{constant}, \; qemax = \text{constant}, \end{aligned} \qquad [2.8]$$

where $qemax$ is the maximal amount of drug that the organism can burn per time unit. It now follows from [2.4], [2.5] and [2.8] that

$$\begin{aligned} \dot{c}(t) \stackrel{\text{mod}}{=}\; & a_1 cs(t) - qemax/V \\ & \times (1 - \text{Exp}[-a_2 c(t) V/qemax]). \end{aligned} \qquad [2.9]$$

Eqs. [2.6] and [2.9] together with the external given function $qi(t)$ are the main equations and are used in the simulations in the following section.

SIMULATIONS

This section illustrates typical simulations of the model compared with in vivio experiments with digitoxin. The model matches the experiments very well. By running the theoretical model 20 days into the future we foresee the dynamics of the drug concentration.

In order to run simulations we need the parameters V, a_1, a_2 and $qemax$. Different organisms will in general need different values for the parameters. Also the parameters are for a given organism dependent of the type of drug used. The volume is approximately equal to the water content in the organism: 0.6 mass of body/density of body. For a human body the 'digestion time' $1/a_1$ is generally in the order of hours. The 'metabolic time' $1/a_2$ depends very much on the type of drugs used, and can be from ours to some days. For all simulations we will assume that $qemax(1 - \text{Exp}[-a_2 m(t)/qemax]) \approx a_2 m(t)$. Then it is unnecessary to specify $qemax$.

In Fig. 1 we see the input function $qi(t)/V$ in nanograms per milliliter per day (ng/ml/day). The first day we insert 0.6 millgrams of digitoxin over a very short time interval (minutes). The next day we insert 0.4 millgrams over the same time interval. The next day we insert 0.1 milligrams

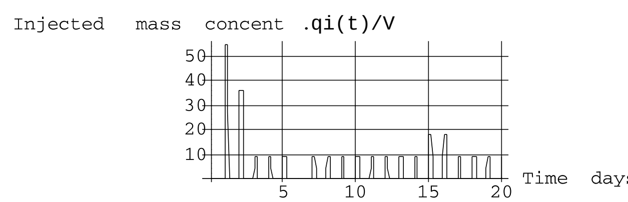

Fig. 1 The injected mass of digitoxin per volume per time unit (ng/ml/day) as a function of time. $V = 5.53 \times 10^4$ ml, $a_1 = 10/\text{day}$, $a_2 = 0.071/\text{day}$.

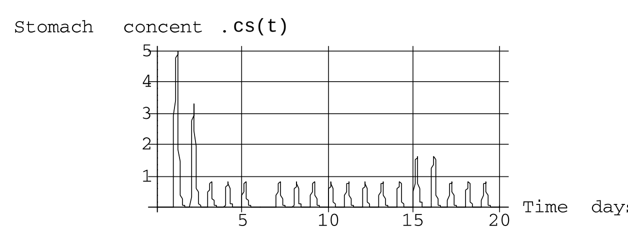

Fig. 2 The mass of digitoxin in the stomach per volume (ng/ml) as a function of time. $V = 5.53 \times 10^4$ ml, $a_1 = 10/\text{day}$, $a_2 = 0.071/\text{day}$.

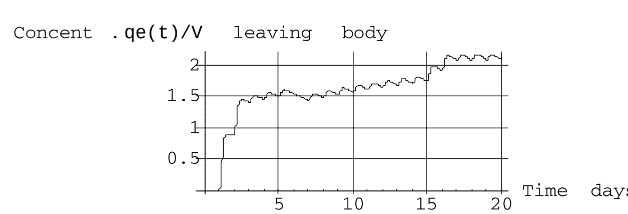

Fig. 3 The mass of digitoxin leaving the body per time unit and per volume (ng/ml/day) as a function of time. $V = 5.53 \times 10^4$ ml, $a_1 = 10/\text{day}$, $a_2 = 0.071/\text{day}$.

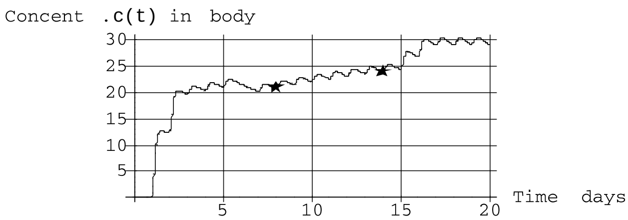

Fig. 4 The concentration of dixitoxin (ng/ml) as a function of time. $V = 5.53 \times 10^4$ ml, $a_1 = 10$/day, $a_2 = 0.071$/day.

and so on. Notice that for day 6 we do not insert anything and that for days 15 and 16 0.2 milligrams are inserted.

In Fig. 2 we see the stomach concentration $cs(t)$ (ng/ml) as a function of time. Observe that the stomach is nearly empty before a new drug injection is provided.

Fig. 3 shows the amount of digitoxin leaving the organism as a function of time. Observe that the theoretical equilibrium level is approximately 2 ng/ml/day.

In Fig. 4 we see the plasma concentration $c(t)$ of digitoxin as a function of time. Also shown with two stars are the experimental values and which are in good agreement with the theoretical values.

CONCLUSION

During treatment of a living organism infected by cancer through the use of chemotherapy, it is important to foresee the therapeutic concentration in the organism as a function of the therapeutic dose. For many drugs, e.g., digitoxin, the difference between the therapeutic concentration and the toxic concentration is very small. The ability to foresee the concentration level is particularly important. This article provides a mathematical dynamic description of the interaction between the organism and the drug, and where the dynamics are analysed using ordinary differential equations. The model is tested in a clinical situation where digitoxin is used as the therapeutic drug. The agreement with in vivo experiments is good.

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REFERENCES

1. Stenkvist B., Bengtsson E., Erikson O., Holmquist J., Nordin B., Westman-Naeser S. Cardiac glyco-sides and breast cancer. *Lancet* 1979; **1**: 563.
2. Haux J., Lam M., Marthinsen A. B. L., Strickert T., Lundgren S. Digitoxin, in non toxic concentrations, induces apoptic cell death in Jurkat T cells in vitro. *Originalia Z Onkol/J of Oncol* 1999; **31**(1): 14–20.