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Mathematical modelling of tumor growth in mice following electrotherapy and bleomycin treatment

Damijan Miklavčič [a], Tomaž Jarm [a], Rihard Karba [a,*], Gregor Serša [b]

[a] *Faculty of Electrical and Computer Engineering, University of Ljubljana, Tržaška c. 25, 61000 Ljubljana, Slovenia*
[b] *Institute of Oncology, Zaloška c. 2, 61000 Ljublijana, Slovenia*

Abstract

In treatment of subcutaneous solid tumors in mice locally applied electrotherapy by direct current and i.v. administered bleomycin were combined. The study showed the interaction of both treatments in a way, that the antitumour effect of both was more than additive when compared to single treatments. The electrotherapy by means of 0.6 mA of one hour duration, as single treatment significantly delayed tumour growth in comparison to control group (growth delay GD = 6.7 ± 1.2 days), whereas therapy by 250 μg bleomycin i.v. injection had only moderate effect on tumour growth (GD = 0.5 ± 0.2 days). When both treatments were combined the tumour growth delay observed was 10.8 ± 1.9 days. A model was developed in which the pharmacokinetic model of bleomycin was extended and transformed to the level of macroscopic biologically detectable effect i.e. tumour growth retardation. The data on tumor growth in control group was used to determine parameters of the Gompertz model (V_0, α_{v0} and β). For modelling of both single treatments the extended Gompertz equation was used. In the case of electrotherapy a two component effect had to be introduced in order to obtain satisfactory fit. The effect of bleomycin on tumour growth was obtained by introducing the influential parameter which transferred the bleomycin concentration in tumour tissue obtained from pharmacokinetic model to the effect on tumour growth.

1. Introduction

Subcutaneous solid tumors in mice were treated by means of locally applied electrotherapy (ET) by direct current and intravenously administered bleomycin. In the study reported in detail previously [4] subcutaneously grown solid tumors were treated by either single shot (i) intravenous injection of 250 μg of bleomycin into the tail vein; (ii) electrotherapy of one hour duration, direct current 0.6 mA; or (iii) combination of both, after the tumors reached 30–40 mm^3. In order to asses the effectiveness of single and combined treatments, tumor volumes were determined by measuring three tumor mean diameters (a, b and c) and by calculating

* Corresponding author

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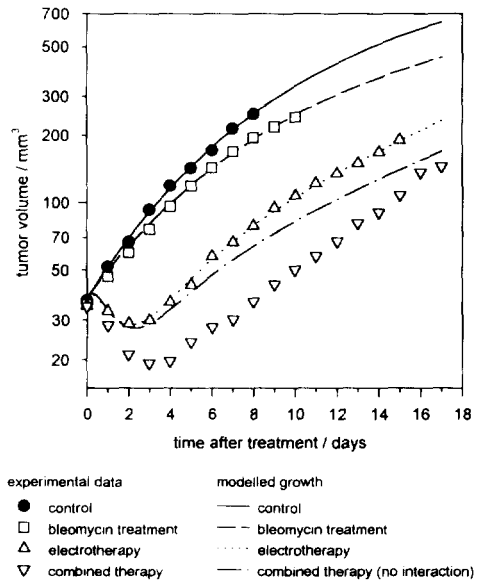

Fig. 1. Experimental data and modelled growth curves.

tumor volume according to formula $V = \pi abc/6$. The results were compared to tumor growth in control group where electrodes were placed subcutaneously near the tumors and physiological saline was injected in the tail vein exactly as in previously described experimental groups. Tumor growth data thus obtained are presented in Fig. 1. The electrotherapy as single treatment significantly delayed tumor growth in comparison to control group, whereas bleomycin therapy had only moderate effect on tumor growth. The tumor growth delay was calculated as a difference of mean tumor doubling times in therapy and control experimental groups. Tumor doubling time was determined for each individual tumor as the time needed to double the initial tumor volume. The tumor growth delay was 6.7 ± 1.2 days ($\nu = 15$) (AM $\pm$ STD (degrees of freedom)) in electrotherapy group and 0.5 ± 0.2 days ($\nu = 12$) in group subjected to bleomycin treatment. When both treatments were combined the tumor growth delay observed was 10.8 ± 1.9 days ($\nu = 16$), i.e. the effects were more than additive.

The objective of the study was to model tumor growth after different treatments performed, and to extend the pharmacokinetic model of bleomycin to the pharmacodynamic model, i.e. to asses tumor growth retardation based on the bleomycin pharmacokinetic model. Coupled model of both treatments should produce an additive effect of both single treatments performed.

2. Development of the model

The development of a model required four major steps. First the most convenient model for undisturbed tumor growth was sought, which served as a basis for further work. In next steps

this model was modified by introducing the parts which reflected the influences of both therapies.

2.1. Undisturbed (control) tumor growth

Four widely used growth equations were put under investigation [5,7]. These were exponential, Gompertz, Bertalanffy and Verhulst (logistic) equation (Eqs. 1, 2, 3 and 4). In all of them V represented tumor size (volume) and V_0 was its initial size at the beginning of observation. The values of the parameters in the equations were determined upon fitting them to actual growth data.

$$\frac{dV}{dt} = \lambda V, \qquad V(0) = V_0, \tag{1}$$

$$\frac{dV}{dt} = V\left(\alpha_{V_0} - \beta \ln\frac{V}{V_0}\right), \qquad V(0) = V_0, \tag{2}$$

$$\frac{dV}{dt} = \eta V^{2/3} - \mu V, \qquad V(0) = V_0, \tag{3}$$

$$\frac{dV}{dt} = aV - bV^2, \qquad V(0) = V_0. \tag{4}$$

In the comparative study the growth equations were fitted to the average tumor growth data of the control group and also to the growth data of individual tumors in this group. Several numerical criteria were used to estimate model suitability, the most important being goodness of fit and predictability of the model [6]. The goodness-of-fit parameter r^2 was calculated according to equation 5 [2] where x_i and $\hat{x}_i$ were the i-th measured and estimated size of the tumor respectively. The fit was proclaimed to be satisfactory when $r^2 > 0.98$ (higher r^2 meaning better fit). The predictability was assessed by fitting a model to first m out of n measured experimental points and by calculating the prediction error for the rest of n-m points.

$$1 - r^2 = \frac{\sum_{i=1}^{n}(\hat{x}_i - x_i)^2}{\sum_{i=1}^{n} x_i^2 - \frac{1}{n}\left(\sum_{i=1}^{n} x_i\right)^2}. \tag{5}$$

The exponential equation did not meet our requirements at all. The rest of the models gave similar results with the Gompertz model being moderately more suitable. In a few individual cases when either the Bertalanffy or the logistic equation gave the best fit or prediction, the Gompertz one was always very close to them. When fitted to some of the individual tumor growth data the optimisation produced degenerated versions of the Bertalanffy or the logistic model since their parameters tended to go to zero or even negative values. Reaching global minimum of error function during optimisation of these two models also caused much more trouble than optimisation of the Gompertz model which was thus chosen for further modelling. The result of fitting of the Gompertz model to the control group data is shown in Fig. 1 ($r^2 = 0.999$).

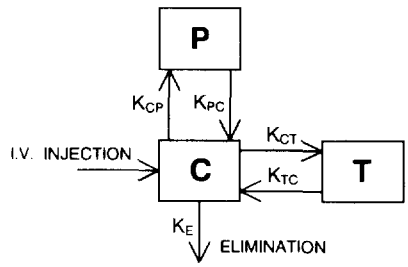

Fig. 2. Three-compartment model.

2.2. Bleomycin pharmacokinetics

Bleomycin concentration in blood plasma decreases biexponentially after intravenous bolus injection. This can be described by a linear non physiological two-compartment model (central and peripheral compartment) [1]. The central compartment represents the blood and all with bleomycin well perfused tissues. The peripheral compartment represents the rest of the body. Since our goal for the future was to find the level of interaction between electrotherapy and therapy with bleomycin, we split the peripheral compartment into two parts, the first for the tumor (T) and the second for the rest of the periphery (P), as shown in Fig. 2. Bleomycin is cleared from the body mostly by renal elimination which is modelled by secretion from the central (C) compartment [1]. Fig. 3 shows quantity/time curves of bleomycin in central and peripheral compartments.

2.3. Introducing bleomycin treatment

To exert their cytotoxic properties the bleomycin molecules have to enter the tumor cells, where they damage cellular DNA [3]. It seemed highly inappropriate to introduce the

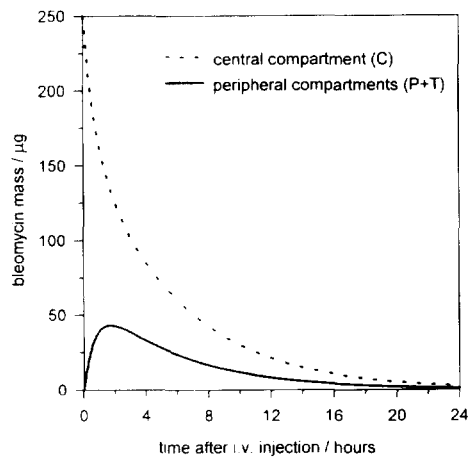

Fig. 3. Quantity of bleomycin in central and peripheral compartment.

concentration of bleomycin directly into the growth model since there had to be some delay between bleomycin entering the cells and the changing of tumor growth rate. Therefore a new quantity was introduced into our model, namely the influence of bleomycin therapy ($BT(t)$), which was related to the bleomycin concentration through the first order delay. Eq. 6 describes tumor growth after treatment with bleomycin. Its optimised form gives the fit to the experimental data of the group of mice treated with bleomycin as shown in Fig. 1 ($r^2 = 0.997$).

$$\frac{dV}{dt} = V\left(\alpha_{V_0} - \beta \ln\frac{V}{V_0} - \gamma BT(t)\right), \qquad V(0) = V_0. \tag{6}$$

2.4. Introducing electrotherapy

The influences of electric current were introduced into the Gompertz model in a similar way as those of bleomycin. Again it was necessary to use delay between the current itself and its visual effect, that is altered rate of tumor growth. The modelling showed however, that at least two components had to be added to the original form of the Gompertz equation in order to obtain a satisfactory fit to the experimental data of the third group of mice. These two components ($ET_1(t)$ and $ET_2(t)$) had the third and the second order delay respectively with reference to electric current with $ET_1(t)$ and $ET_2(t)$ having pronounced influence in the late and in the early stage of observation respectively. This suggests that at least two important mechanisms were involved in antitumor effectiveness of weak DC electric current. Eq. 7 presents the modified Gompertz model of tumor growth after electrotherapy. The result of the optimised model is shown in Fig. 1 ($r^2 = 0.999$).

$$\frac{dV}{dt} = V\left(\alpha_{V_0} - \beta \ln\frac{V}{V_0} - \eta_1 ET_1(t) - \eta_2 ET_2(t)\right), \qquad V(0) = V_0. \tag{7}$$

2.5. Modelling combined treatment

By joining the modified models of tumor growth after single therapies the model of tumor growth after combined therapy was obtained based on assumption that there was no interaction between the therapies. Fig. 1 clearly shows that this additive coupling of both therapies in a model does not fit to the experimental data of the group of mice submitted to both therapies where tumor retardation was far more pronounced than suggested by our model.

3. Results

The Gompertz model was used for easiness of introduction of therapeutic effects and convergence in optimisation experiments. The data on tumor growth in control group was used to determine parameters of Gompertz model V_0, α and β. For both single treatments, electrotherapy and bleomycin, extended Gompertz equation was used. In the case of electrotherapy a two component effect with different time constants and second order delay of

action had to be introduced in order to obtain satisfactory fit. The effect of bleomycin treatment on tumor growth was obtained by introducing the influential parameter which transferred the bleomycin concentration in tumor tissue obtained from pharmacokinetic model to the effect on tumor growth. The prediction of additive effect of both treatments joined in the model proved to underestimate the experimentally gained combined treatment effectiveness. It is the objective of our future work to evolve the model of interaction of both treatments, electrotherapy and treatment by bleomycin.

Acknowledgement

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