Vidyodaya J. Sci., (1991) *Vol.* 3, *No* 2, pp. 129-132

A MATHEMATICAL MODEL OF DRUG THERAPY

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Abstract

A problem discussed by Burghes, Huntley and McDonald (1, *pages* 124—129) *relating to Drug Therapy is shown to be a very critical case of a general formulation of the problem. It is also shown that their prescription to give a dose of* 250*mg every* 4 *hours is alright if it is confined to about* 24 *hours, but, if it is dane for a longer period, the patient will suffer due to an overdose of the drug. The case is critical because their upper tolerance level of* 20 *mg/litre is exactly* 4 *times their lower tolerance level of* 5 *mg/litre.*

The problem discussed is the following. A patient whose mass is 50kg has to be given a certain drug in fixed dosages at regular intervals. If the drug concentration in the blood is less than 5mg/litre, it is ineffective whereas, if it exceeds 20mg/litre, it is likely to be toxic. They assume that, in between administrations of the drug, the rate at any time at which the concentration of the drug decreases with time is proportional to the concentration of the drug at that time. Thus, if the initial concentration of the drug is C_o, then, after time t before administering the next dose, the concentration $c(t)=c_o e^{-kt}$. Their value of $k=0.17$ hour^{-1}.

Their prescription to give 250mg every 4 hours amounts to an initial concentration of 10mg/litre. Taking $c_o = 10$, the following table can be constructed for the maximum and minimum concentrations, corresponding to the concentrations just after and just before a dose is given.

Time range	**Maximum concentration**	**Minimum concentration**
hours	**mg/litre**	**mg/litre**
$0 \leqslant t < 4$	10	$10e^{-.17 x 4}$ $= 10e^{-.68}$
$4 \leqslant t < 8$	$10 + 10e^{-.68}$ $= 10(1 + e^{-.68})$	$10(1 + e^{-.68})e^{-.68}$
$8 \leqslant t < 12$	$10 + 10e^{-.68}(1 + e^{-.68})$ $= 10(1 + e^{-.68} + e^{-2x.68})$	$10e^{-.68}(1 + e^{-.68} + e^{-2x.68})$

For the nth period of 4 hours, the data will be as follows.

$$4(n-1) \leqslant t < 4n \qquad 10\frac{1 - e^{-.68n}}{1 - e^{-.68}} \qquad 10e^{-.68}\frac{1 - e^{-.68n}}{1 - e^{-.68}}$$

The maxima increase as time goes on and tends to $\dfrac{10}{1 - e^{-.68}}$ as $t \longrightarrow \infty$. This value is 20.27 which is over the upper limit of 20 prescribed.

The lowest concentration is the lowest of the minima, which is $10e^{-.68} = 5.07$. Thus, the drug concentration level never goes below the lower limit prescribed but goes above the upper limit prescribed beyond which, it is claimed by them, that it may be toxic. It is interesting to find out how soon the upper limit is exceeded. For this purpose, the actual values have been worked out, and they are as follows.

Time Range hours	**Maximum Concentration** mg/litre
$0 \leqslant t < 4$	10
$4 \leqslant t < 8$	15.07
$8 \leqslant t < 12$	17.63
$12 \leqslant t < 16$	18.93
$16 \leqslant t < 20$	19.59
$20 \leqslant t < 24$	19.92
$24 \leqslant t < 28$	20.09

Since the maxima keep on increasing with time, it is seen that if the drug is stopped in one day, then, the drug concentration does not go outside the range of tolerance, but, if it is continued beyond that, the maximum concentration goes beyond the upper limit. After the 7th dose is given, the concentration exceeds the upper limit prescribed and thereafter, each time a dose is given, the concentration exceeds the upper limit prescribed.

A general discussion of this particular model shows that it satisfies the condition that the upper tolerance level is exactly four times the lower tolerance level. In such a case, there is only one solution to the problem irrespective of the value of the constant k in the expression

$$c(t) = c_o \, e^{-kt},$$

as the following discussion shows.

Let the lower limit of concentration be p and the upper limit be q. Then the requirements are

$$c_0 e^{-kT} \geqslant p, \quad \ldots\ldots\ldots\ldots \quad (1)$$

$$\text{and} \quad \frac{c_0}{1 - e^{-kT}} \leqslant q, \quad \ldots\ldots\ldots\ldots \quad (2)$$

where a dosage of concentration c_0 is given at periodic intervals of length T.

$\frac{c_0}{1 - e^{-kT}}$ is the sum of an infinite geometric series and therefore this concentration is never reached in practice. However, since calculations are done only to a particular number of decimal points, it may be assumed that this concentration is reached as soon as $\frac{c_0 e^{-nkT}}{1 - e^{-kT}}$ becomes negligible with increasing n.

The inequalities (1) and (2) imply

$$c_0 \geqslant pe^{kT},$$

$$\text{and} \quad c_0 \geqslant q(1 - e^{-kT}).$$

For there to be a suitable value for c_0, it is necessary that

$$pe^{kT} \leqslant q(1 - e^{-kT})$$

$$\therefore \; e^{2kT} - \frac{q}{p} e^{kT} + \frac{q}{p} \leqslant 0$$

$$\therefore \; (e^{kT} - \frac{q}{2p})^2 \leqslant \frac{q^2}{4p^2} - \frac{q}{p}$$

$$= \frac{q}{4p^2} (q - 4p).$$

Thus, if $q < 4p$, it is not possible to prescribe a fixed dose to be given periodically with a constant period.

If $q = 4p$, as in the case discussed by Burghes et. al., (1, pages 124-129), then, the above condition can be satisfied only if

$$e^{kT} = \frac{q}{2p} = 2.$$

$$\therefore \; T = \frac{1}{k} \ln 2.$$

The concentration c_0 is then fixed at 2p.

If $q > 4p$, then, there is a range of suitable values for e^{kT}. It may turn out to be possible to select T to be a factor of 24 or even a multiple of 24 so that the drug administration becomes simpler.

References

1. D. N. Burghes, I. Huntley and J. McDonald:
Applying Mathematics, A course in Mathematical Modelling. Ellis Horwood Limited (1982).