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# S2 Appendix. Prophylaxis regimens that maximize the lowest factor VIII concentration

When seeking to identify prophylaxis regimens that maximize the lowest factor VIII concentration we can ignore the (constant) endogenous factor concentration, *E*, by setting it to 0. Then trough concentrations satisfy the relation

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where *tj* is the end of the cycle and *Δti+1 = ti+1 – ti*. Rearranging yields

 (Equation A2.1)

and summing the *Di* to obtain the total dose in a cycle gives

From the former summation pull out the *i = j* term and from the latter pull out the *i = 0* term, so

In the steady state *G0 = Gj*, so

Let . Then

 (Equation A2.2)

Consider the scenario in which the total dose and the injection schedule are fixed but the total dose can be shared between injections in any way. Note that fixing the injection schedule fixes the values of *ci*. Equation A2.2 shows that if there exists a regimen that shares doses across injections in a way which makes all of the troughs in a cycle equal (i.e., which makes all *Gi = G*) that regimen is the regimen that maximizes the lowest factor VIII concentration. This must be true because it is not possible that all of the troughs *Gi > G*; otherwise, if all *Gi > G,* then , which is inconsistent with Equation A2.2 because it is then not possible that both and both equal *D*. Thus, for any given injection schedule, the regimen which maximizes the lowest factor VIII concentration is the regimen that makes the troughs equal, if such a regimen exists.

A regimen that makes the troughs equal always exists. This can be demonstrated by making all the trough values *Gi = G*. Then, from Equation A2.1

 (Equation A2.3)

Summing across *i* gives

 (Equation A2.4)

This is the trough concentration that is attained when all of the troughs are equal, so it is also the trough concentration when the regimen is optimal (in the sense of maximizing the lowest factor VIII concentration) for a given injection schedule. Substituting Equation A2.3 into A2.4 gives

The quantity in the square brackets is the proportion of *D* that is *Di*. It has a value between 0 and 1, so *Di* has a value between 0 and *D*. To the extent that it is possible to give injections with doses of anywhere between 0 and *D*, this implies that there always exists a regimen that makes the troughs equal, so there is always a regimen that maximizes the lowest factor VIII concentration for any injection schedule. In practice it may be difficult to administer that optimal regimen.

The preceding part of this appendix shows that the optimal regimen *for a given injection schedule* is a regimen which shares the total dose across injections in a way that makes all trough concentrations equal. Now we allow the injection schedule to vary and we ask which of all possible regimens with dose *D* and number of injections *j* maximizes the lowest factor VIII concentration. We can conceive of the injection schedule (the set of *Δti*) as an independent variable and the trough concentration *G = G(Δti)* to be a function of the injection schedule (Equation A2.4) subject to the constraint that .

The method of Lagrangian multipliers shows that *G* is maximized when *∂ G/∂ Δti = λ*, where *λ* is the Lagrangian multiplier. Rearranging gives *∂ Δti = ∂ G/λ*. Note that the expression for *∂ Δti* does not depend on *i*. This shows that when *G* is maximized, *Δti* is constant (i.e., all *Δti* are equal). So, of all possible injection schedules, the lowest factor VIII concentration is maximized when the intervals between injections are equal. We have already seen that if the lowest factor VIII concentration is to be maximized the trough concentrations must be equal. And if both the intervals between injections are equal and the trough levels are equal, the doses of each of the injections must also be equal. So, of all possible injection regimens, the lowest factor VIII concentration is maximized when the intervals between injections are equal and the doses of the injections are equal.

In the preceding paragraph we fixed the number of doses. What is the optimal number of doses? Since the optimal schedule has equal intervals between injections, *Δti = T/j.* As the number of doses goes to infinity, *Δti 🡪 0*, *so* .

As a consequence,

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and

As *j 🡪 ∞,*  approaches its minimum, which is *T / (τ)*. As a consequence, *G* approaches its maximum at This is the steady state concentration when a continuous infusion is given.