Approaches to optimization of prophylaxis

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Background: Prophylactic intravenous injections of clotting factor reduce the incidence of bleeds and slow the development of joint damage in children with severe hemophilia A. While there has been extensive discussion of how pharmacokinetic considerations might influence dosing in hemophilia prophylaxis there has, to our knowledge, been little systematic investigation of how prophylaxis regimens might be optimized.

Aims: The aim of this study is to identify prophylaxis regimens for people with haemophilia that maximize time above a threshold plasma clotting factor concentration (e.g., 1 IU/dL) and which maximize trough clotting factor concentrations.

Methods: Equations were developed to describe the steady state pharmacokinetics of clotting factor concentrations during a recurring prophylaxis cycle in which injections may have unequal doses and may be administered at unequal intervals. These equations were used to identify prophylaxis regimens that maximize time for which plasma clotting factor concentrations exceed a nominated threshold, and to identify prophylaxis regimens that maximize trough plasma clotting factor concentrations. Grid searches were conducted to identify optima. The grid typically contained ~2.5 million prophylaxis regimens.

Results: Data are shown for prophylaxis with 3 injections weekly totaling 90 IU/kg given to a person with no endogenous clotting factor, a half-life of 10.7 hours, and an in vivo recovery of 2.0.

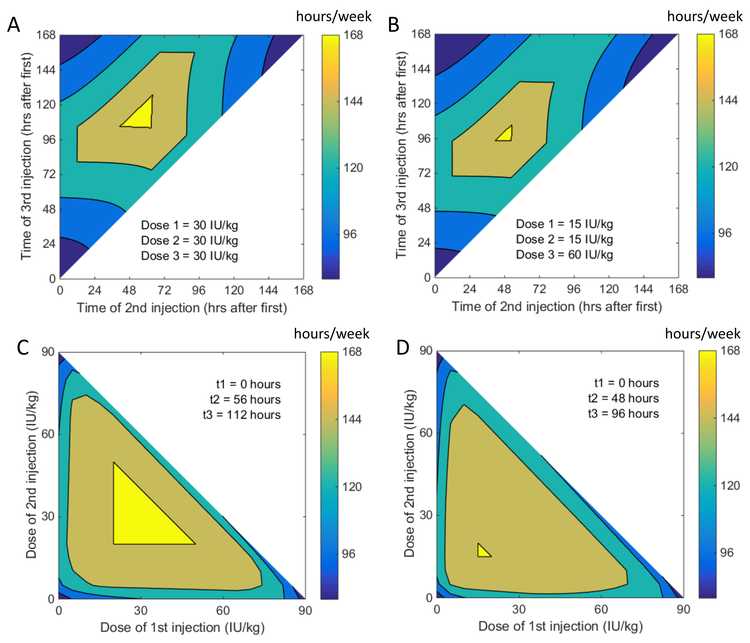

Figure 1. Effect of timing and dose of injections on time above a threshold of 1 IU/dL (hrs/wk). Time of injections is expressed as time of the second and third injection after the first. Panels A and B show the effect of timing of injections when the dose of injections is fixed. Panels C and D show the effect of dose of injections when the timing of injections is fixed. In panels A and C, the dose of all three injections is equal (D1 = D2 = D3 = 30 IU/kg). In panels B and D, the dose of injections is unequal (D1 = D2 = 15 IU/kg; D3 = 60 IU/kg).

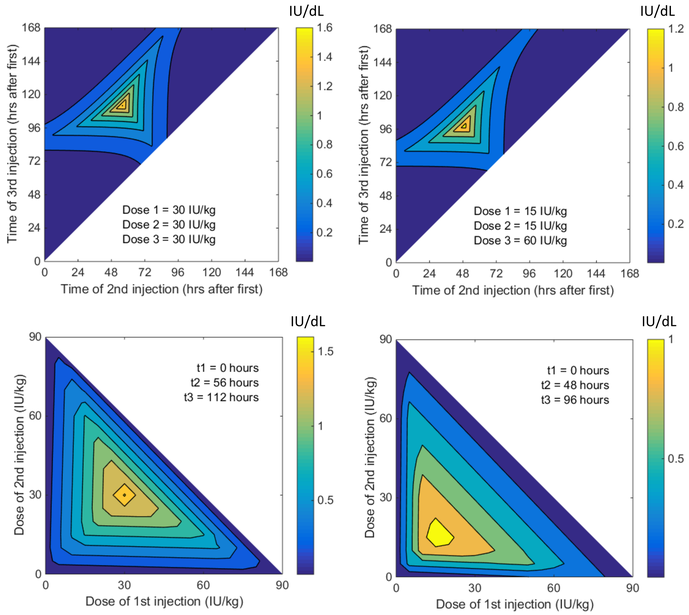

Figure 2. Effect of timing and dose of injections on trough plasma clotting factor concentration (IU/dL). This figure is the same as Figure 1 except that the outcome being optimized is the trough plasma clotting factor concentration.

When the optimal regimen is defined in terms of time above threshold there may be many optima, but when optima is defined in terms of trough clotting factor concentrations there is a unique optimum. The prophylaxis regimen which involved equal doses at equal intervals maximized both time above threshold and the trough clotting factor concentration.

A regimen in which three injections are given at equal intervals in one week is likely to be very inconvenient. The methods described here enable exploration of trade-offs with suboptimal regimens. In the scenarios illustrated here, giving the second and third injections 48 and 96 hours after the first (i.e., at the same time of day) reduced time above threshold from 168 hours per week to 160 hours per week, and reduced trough levels from 1.6 IU/dL to 0.6 IU/dL.

The findings are person-specific, but they suggest some general principles of prophylaxis: if the aim is to maximize trough levels then the optimal regimen involves equal dose injections administered at equal intervals. If injections are to be administered at unequal intervals then the optimal doses will be unequal: the largest dose should be provided before the longest interval. The relationship between the length of an inter-injection interval and the optimal dose of the injection that precedes the interval is complex.

Conclusions: It is possible, using well-accepted assumptions, to identify optimal prophylaxis regimens for people with hemophilia.