Identification of the optimal prophylaxis regimen for a physically active child with severe haemophilia A

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Background: Prophylactic 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 minimize the incidence of bleeds.

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 combined with equations relating the incidence of bleeds to clotting factor concentration. Two alternative equations were used. The first equation, developed by Collins et al (2009), expresses the incidence of bleeds as a function of hours per week spent with a clotting factor concentration > 1 IU/dL. The second equation, developed by Broderick et al (2012), related bleeds incidence to the instantaneous clotting factor concentration and physical activity levels. Grid searches were conducted to identify optimal prophylaxis regimens.

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

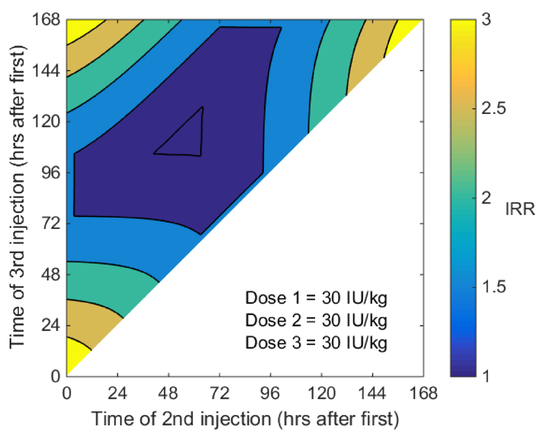

Figure 1. Optimal prophylaxis regimens identified with the Collins model. The optimal prophylaxis regimen identified using the Collins model was one in which equal doses were given at equal intervals (i.e., the second and third injections were given 56 and 112 hours after the first). This figure shows the effect on the incidence rate ratio of changing the timing of injections while keeping the dose constant for all three injections. A regimen in which injections are given at the same time of day (48 and 96 hours) is suboptimal: it is associated with 12.5% greater risk than the optimal regimen.

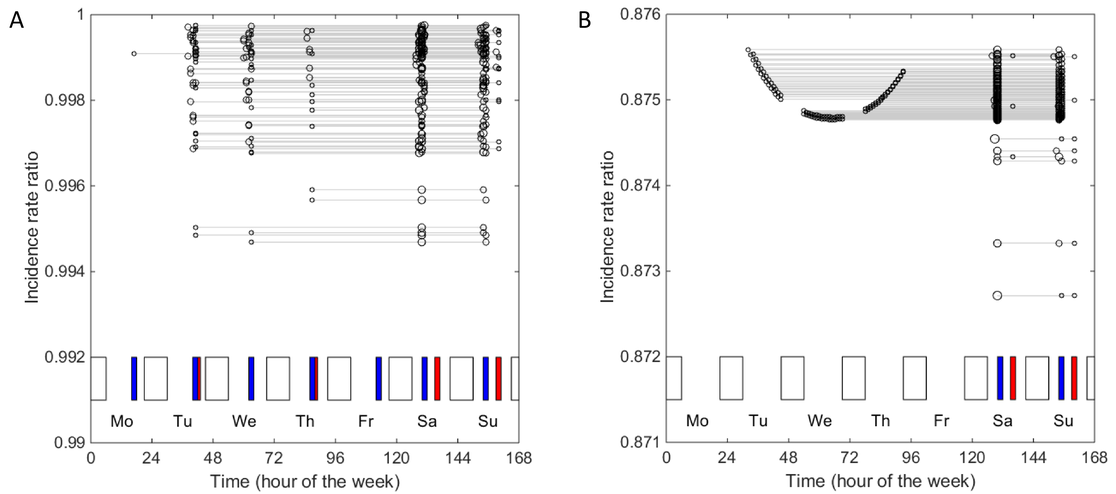

Figure 2. Optimal prophylaxis regimens identified with the Broderick model for A, a 'very active' person and B, a 'weekend active' person. Patterns of physical activity are shown as bars in the lower part of each panel. Blue bars are periods of medium risk activity and red bars are periods of high risk activity. Unfilled bars are periods of sleep. Each of the 100 prophylaxis regimens that best minimize bleeds incidence is shown as a horizontal line joining symbols that indicate the time of injections. Zero time is midnight on Sunday night. The size of the circles indicates the dose (smallest 15 IU/kg, intermediate 30 IU/kg, largest 45 IU/kg).

Some general observations arise from the simulations conducted using these models. First, prophylaxis regimens that maximize pharmacokinetic parameters (such as time above a threshold plasma clotting factor concentration) and their derivatives (such as bleeds incidence estimated with Collins' model) may be very different to the prophylaxis regimens that minimize the incidence of bleeds. Second, when people participate in risky physical activities, the optimal regimen usually involves injections given prior to periods of activity. If most risky physical activity occurs late in the day the optimal prophylaxis schedule often involves injections in the afternoon.

Our preliminary experience is that there are often many prophylaxis regimens that are close to optimal. When that occurs it would be reasonable to select the most convenient regimen from amongst those that are near-optimal.

Conclusions: It is possible to identify prophylaxis regimens that minimize bleeds incidence in people with haemophilia. Prophylaxis regimens which minimize bleeds risk may be very different from prophylaxis regimens that maximize pharmacokinetic parameters..

References:

Collins PW et al (2009) Journal of Thrombosis and Haemostasis 7: 413-420.

Broderick CR et al (2012) JAMA 308: 1452-1459.