Modeling time to onset of toxicity in a Phase I cancer clinical trial.

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Abstract

Phase I data on time to toxicity of a new compound to treat early stage cancer are analyzed as time to event data. Several nonlinear models are considered for changes in risk of the toxicity event over time at various dose levels, with dependence changing after treatment ends. Direct hazard modeling, instead a generalized regression model with a certain failure time distribution, is used and shown to allow great flexibility for modeling dose dependency as well as changes over time. This offers a viable compromise between a highly complex and time consuming, mechanistic PK/PD-modeling approach and a less informative, purely empirical approach.

KEYWORDS: Hazard function, Hill equation, pharmacodynamics, time-varying covariates.

1 Introduction

One class of endpoints which is important in clinical trials involves time-to-event data, including the special case of survival analysis. This kind of data is usually modeled using classical parametric (accelerated failure time) or semi-parametric (Cox proportional hazards) models. These approaches lack flexibility because they impose constraints either on the evolution of the hazard over time or on the effect of covariates on the hazard. More general approaches are rare.[1]

In contrast to survival analysis, pharmacokineticists have developed the specialized and sophisticated area of pharmacokinetic/ pharmacodynamic (PK/PD) modeling which has gained momentum in the pharmaceutical industry.[2] These models are mechanistic in nature, describing the behaviour of the drug in the human body, its effect on intermediate and clinical endpoints, as well as within (intra) patient and between (inter) patient variability.

Alternatively, one can develop models which incorporate knowledge about the mechanism of action in a more qualitative and less mechanistic way. These models are usually simpler in nature but may be able to answer some of the questions of interest. However, they provide less understanding of the underlying biological processes operating.

One important area of application of such models is at the design stage of a clinical trial. In silico simulation of the outcome of a trial has received increasing attention in the pharmaceutical industry over the last few years.[3] The main goals of these simulations have been to assess the probability of success of the trial and to explore the influence of known and unknown factors. To achieve this, all available information and knowledge is incorporated in a formalized and structured way into a model of drug action. In many trial simulations, the mechanistic PK/PD models are used and it would be very useful if such models were also available for time to event studies. Usually, significant statistical complexity is involved in this kind of modeling.

In this paper, we use the direct modeling of the hazard[5] to describe the time to onset of toxicity in a Phase I clinical trial. We attempt to develop more mechanistic models, analogous to those used in other areas of PK/PD.

2 The clinical trial

We shall develop a model for the occurrence of a sub-set of side effects during an eight-day, once-daily treatment with drug X as a function of time and dose. Data are from a double-blind Phase I clinical trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of drug X, in which 49 healthy male subjects were included. The drug under development was expected to yield a series of drug-related dermatological adverse events linked to the drug-class to which it belonged. From prior experience with this class of compounds as well as related compounds available on the market, a typical side-effect pattern could be derived. This encompassed skin rash, dryness of skin and skin peeling with or without itch. These adverse events form a readily recognizable cluster so that, for any subject, the onset of dermatological toxicity is assessed as an event or, more precisely, as a change of state.

The trial was dose-escalating in sequential cohorts receiving doses d, 2d, 4d, 6d and 12d once daily for eight consecutive days, followed by a follow-up period to at least 14 days (or longer in case of side-effects). In each cohort, eight subjects were randomized to be treated either with tablets with active drug X (six subjects) or with matching placebo-tablets (two subjects). In total, ten subjects were on placebo and eight subjects on each dose (except seven on 12d). The data used here are the time in days from the first medication intake to the onset of toxicity for each subject which is defined as the onset of one of the adverse events mentioned earlier.

The data are summarized in Table 1. Figure 1 shows the Kaplan-Meier curves for the time to onset of toxicity for each dose group. ¿From this, it is apparent that

- the time to onset decreases with dose with a clear separation between placebo, the highest dose and all intermediate doses;
- in the placebo-group, only one event was observed on the third day of the treatment, whereas in the highest dose group all subjects developed toxicity before the end of the eight-day treatment period. In the lower dose groups, a limited number of events was seen the during

Table 1: Summary of the incidence and timing of skin toxicity.

	Number of subjects	Number of events on days 1-8	Number of events on days 9–12	Total number of events
Placebo	10	1	0	1
d	8	3	0	3
2d	8	2	3	5
4d	8	1	3	4
6d	8	2	2	4
12d	7	7	0	7

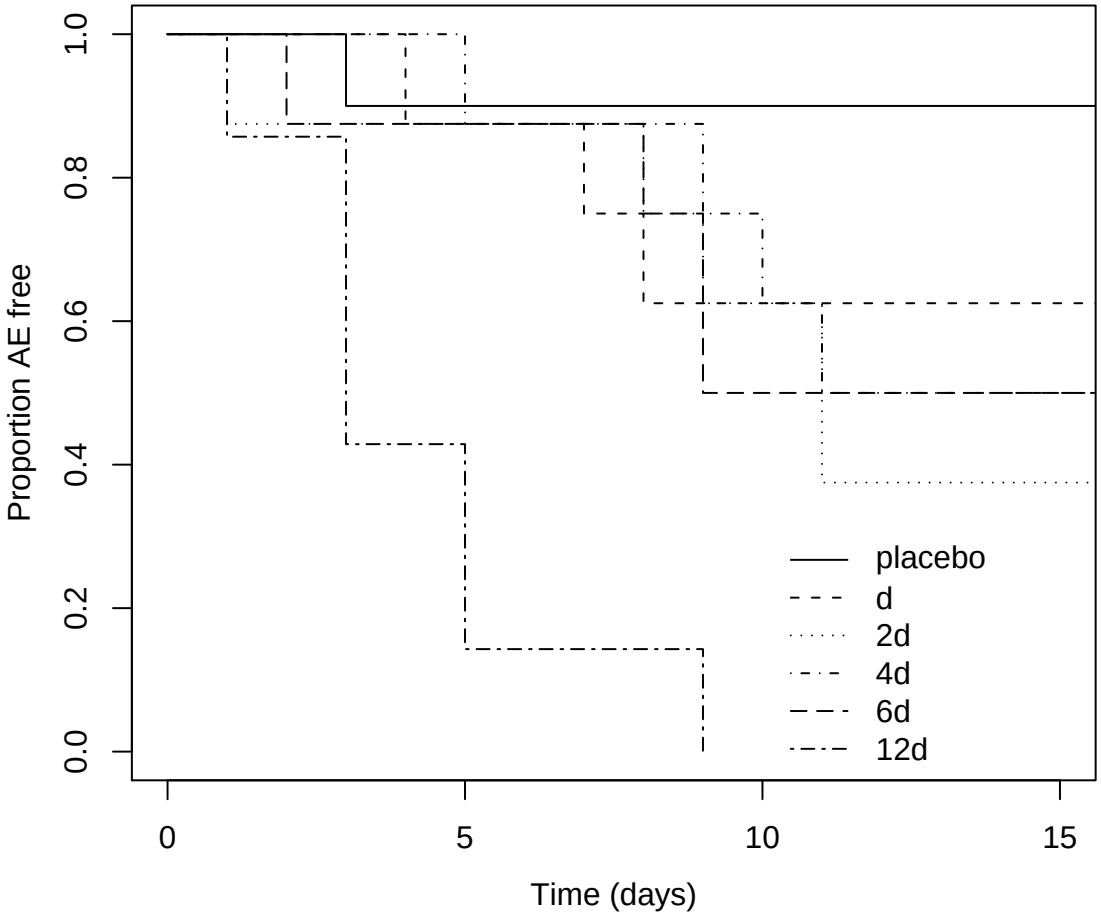

Figure 1: Kaplan-Meier curves for the time to onset of toxicity in the different treatment groups.

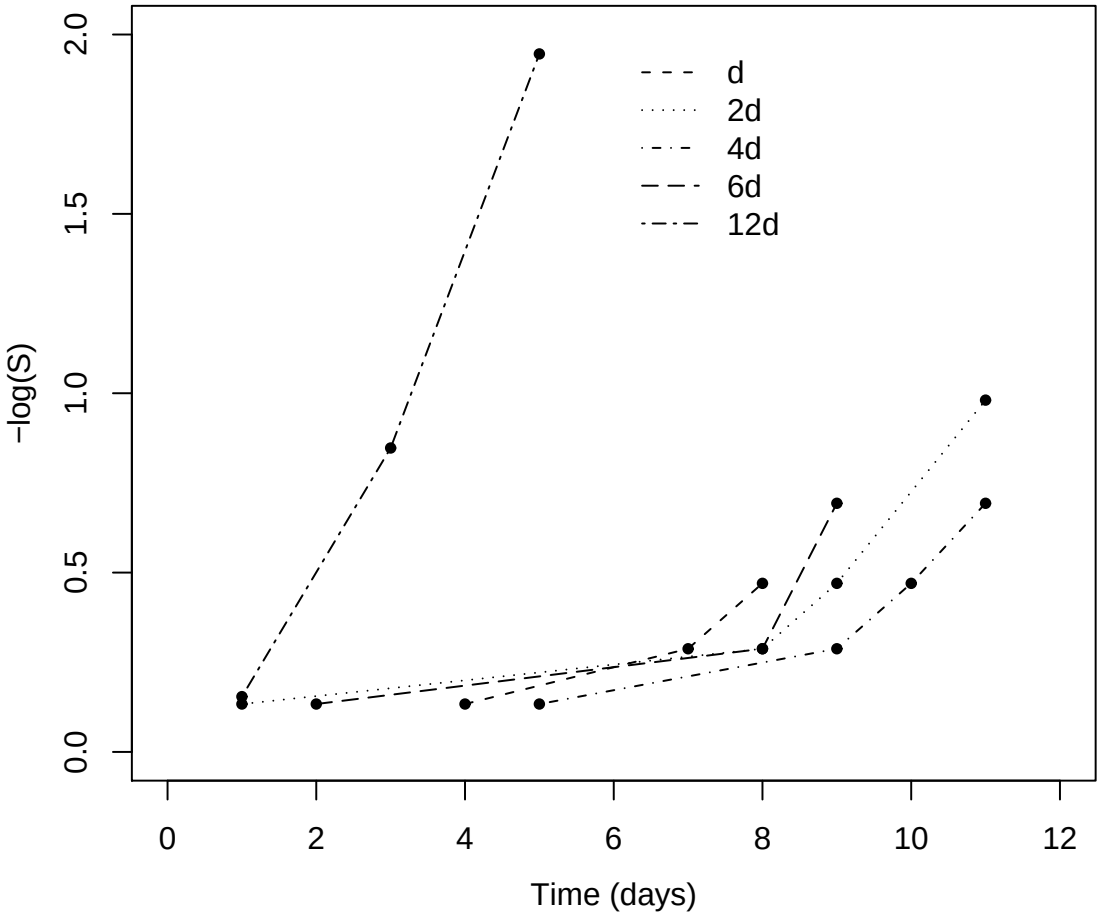

Figure 2: Cumulative hazard plot for the onset of toxicity for the different treatment groups (S(t) is the Kaplan-Meier survival estimate).

first four days of treatment, while a number events happened between days 9 and 12 after the end of treatment.

Figure 2 shows a plot of the cumulative hazard for each treatment group. This plot shows a hazard increase over time for the dose groups lower than 12d, which is sustained for several days after the end of the treatment (day 8).

¿From these observations it is clear that the model should accommodate the following features:

- the hazard increases during the 8-day treatment; the rate of increase seems dose-dependent with a very low or maybe zero hazard during the first days of treatment;
- the hazard does not fall to zero for at least several days immediately after the end of treatment.

Both features are compatible with the pharmacokinetic and pharmacological characteristics of drug X. During the first days of treatment, plasma levels of the drug might be too low to have any toxic effect. Distribution of the compound into the tissues might be another cause for the delay in onset

Table 2: Summary of the model fits.

	Dose-dependence for $\log\lambda$	Time-dependence for $\log\lambda$ during treatment	Time-dependence for $\log\lambda$ after treatment	Number of parameters	AIC
1	None	None	None	1	112.1
2	Factors	None	None	6	103.6
3	Linear	None	None	2	101.9
4	Exponential	None	None	2	102.6
5	Linear	None	Linear Decay	3	94.1
6	Exponential	None	Linear Decay	3	94.2
7	Linear	None	Exponential Decay	3	93.0
8	Exponential	None	Exponential Decay	3	93.1
9	Linear	3-parameter Hill	Linear Decay	5	94.2
10	Linear	2-parameter Hill	Linear Decay	4	93.2
11	Linear	2-parameter Hill	Exponential Decay	4	91.8
12	Exponential	2-parameter Hill	Linear Decay	4	93.8
13	Exponential	2-parameter Hill	Exponential Decay	4	92.6
14	Linear	Linear	Linear Decay	4	92.1
15	Linear	Linear	Exponential Decay	4	91.0

of toxicity. The delay might also be explained by the normal differentiation cycle of the skin cells. Drug X affects the basal layers of the skin, whereas the side effects only become apparent when these cells reach the surface of the skin. After treatment is stopped, plasma and tissue levels will gradually decrease over time. Therefore the risk of toxicity will also gradually decrease as all drug is eliminated from the body.

In order to incorporate these features into the model, we choose to model the hazard as a function of time and dose instead of fitting a generalized regression model with different failure time distributions. Event history modeling also allows the time to recovery from toxicity to be easily included, although this will not be attempted here.

3 Model development

3.1 Time-invariant models

In this first set of models, the hazard is assumed to be constant during the total observation period. This is clearly an oversimplification, but these models are considered as the simplest ones possible with which more complex ones can be compared. The model with a constant hazard independent of time and dose has one parameter and an AIC of 112.1 (Table 2). A model with six parameters, a different constant hazard for each dose, results in a fair drop of the AIC to 103.6. When we consider

these two models as nested, a classical likelihood ratio test yields a 26.9 with 5 d.f. ($p < 0.001$). The (constant over time) hazard thus differs between treatments.

A plot of the hazard estimate as a function of dose (not shown) suggests a linear relationship between the log hazard and dose, at least for the active dose groups. The placebo hazard tends to deviate from this. A linear model has an AIC of 101.9 which is slightly better than the previous one. An exponential model for the log hazard, which might account for the low placebo hazard, is not better (the AIC is higher than for the linear model).

3.2 Time-variant models

3.2.1 Hazard decrease after end of treatment

In these models, the hazard is allowed to decrease after the end of the treatment at day 8. The general form of these models is:

$$\log(\lambda) = f(d) + I(t > t_{\text{end}})g(t - t_{\text{end}})$$

where t is the time (days) since the start of the treatment, d is the dose, and t_{end} is the day of the last medication intake.

Two different models are considered:

1. $\log \lambda$ decreases in a linear fashion with time after the end of treatment:

$$g(t - t_{\text{end}}) = \alpha(t - t_{\text{end}})$$

2. $\log \lambda$ decreases exponentially with time after the end of treatment. Here

$$g(t - t_{\text{end}}) = 1 - \exp(-\alpha(t - t_{\text{end}}))$$

The first model is the simplest. The second makes sense from a pharmacokinetic point of view because this implies an exponential decay of the log risk. Such a decay can be expected on pharmacokinetic grounds if the log risk is directly related to the amount of drug in the body.

In combination with the linear and exponential dose-dependency models from Section 3.1, we consider four models (Table 2, Models 5 to 8). All provide a considerable improvement compared to the time-invariant models although the models with an exponential decay of $\log \lambda$ after end of treatment fit better. There is no difference here between dose-dependency models.

3.2.2 Hazard increases during the treatment period

As it is very plausible that the hazard is not constant during the eight-day period of treatment, it was attempted to model the time-dependency using a Hill-equation.[2] This equation allows to model a flexible range of sigmoid-shaped time courses :

$$\lambda(t) = \frac{\lambda_{\max} t^h}{\lambda_{0.5}^h + t^h}$$

where t is the time (days) since the start of the treatment, $\lambda_{\max}$ is the maximal hazard (asymptote); $\lambda_{0.5}$ is the time at which the hazard equals half of its maximum, and h is the Hill-coefficient which governs the steepness of the increase. After the end of treatment, t retains it value to the last day of the trial. $\lambda_{\max}$ depends on dose either in a linear fashion or in an exponential fashion as before. The general form of the models considered is as follows:

$$f(d,t) = \log(\frac{\lambda_{\max} t^h}{\lambda_{0.5}^h + t^h})$$

A model with a linear dose-dependency and a linear decay (Model 9) is not better than the corresponding one with a constant hazard during treatment (Model 5). However, the estimate of the Hill-coefficient was very close to 1. The same model with $h = 1$ (Model 10) is better than the corresponding Model 5.

Models 10 to 13 correspond to Models 5 to 8 with regard to the dose-dependency and the hazard decay after end of treatment. Here, those with exponential decay fit better. Model 11 is best, also being an improvement over the one with constant hazard during treatment (Model 7).

Although Model 11 fits best of those considered so far, as judged by the AIC, there is a problem with the parameter estimation. The normed likelihood surface (not shown) for the intercept of the linear dose-dependency relation and $\lambda_{0.5}$ shows that the likelihood is extremely flat for the latter parameter. The maximum likelihood estimate is $\hat{\lambda}_{0.5} = 30$ which is implausible because it is far beyond the times observed. This indicates that the asymptote is not estimable so that a simpler model would have a linear trend in time during treatment, resulting in Models 14 and 15. The latter of these, with exponential decay after end of treatment fits best. Although these models fit best, as judged by the AIC, they are probably not realistic. We would not expect the hazard to continously increase during treatment, as this implies that when treating subjects with a low dose or even placebo for a long enough period, everyone will develop toxicity. Extrapolation of the model beyond the current treatment duration must be done with caution anyhow.

The fitted hazard functions for several of these models are plotted in Figure 3. Finally, Figure 4 shows the survival curves, giving the proportion of subjects not having had toxicity, predicted by Model 15 as a function of time and dose.

4 Conclusion

The risk of developing toxicity due to drug X increases with dose during an eight-day treatment. The log of the risk increases linearly with dose implying that the probability of a subject having experienced toxicity at a given time point increases exponentially with dose. After the end of the eight-day treatment, the risk of toxicity remains and gradually decreases to placebo levels in three to four days. There is also evidence that the risk increases during the eight-day treatment period, but the current data do not allow development of a model that adequately describes this.

The use of direct hazard modeling to describe the onset of toxiticy, instead of fitting a generalized regression model with a certain failure time distribution, allows great flexibility for modeling

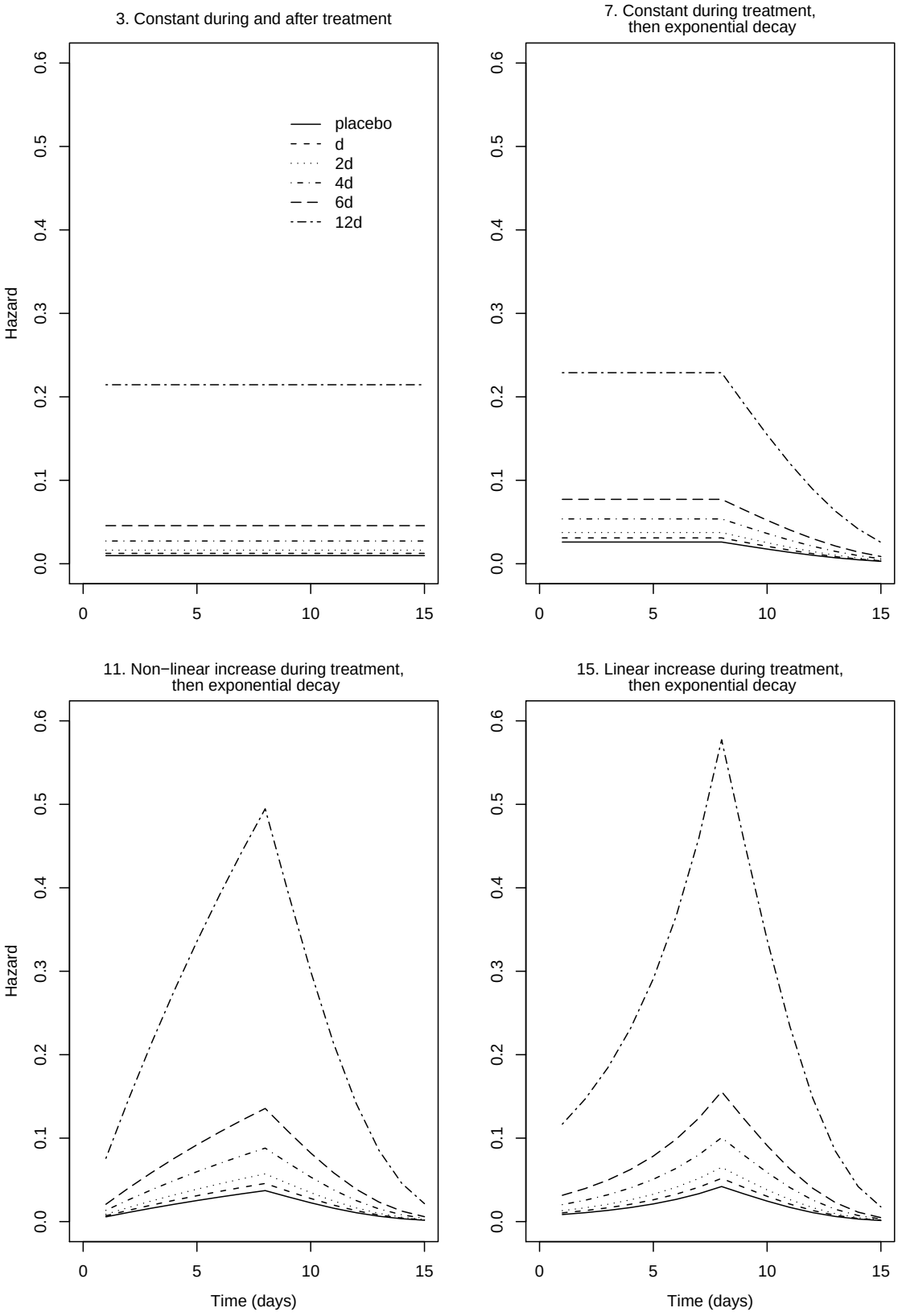

Figure 3: Fitted hazard functions for Models 3, 7, 11, and 15.

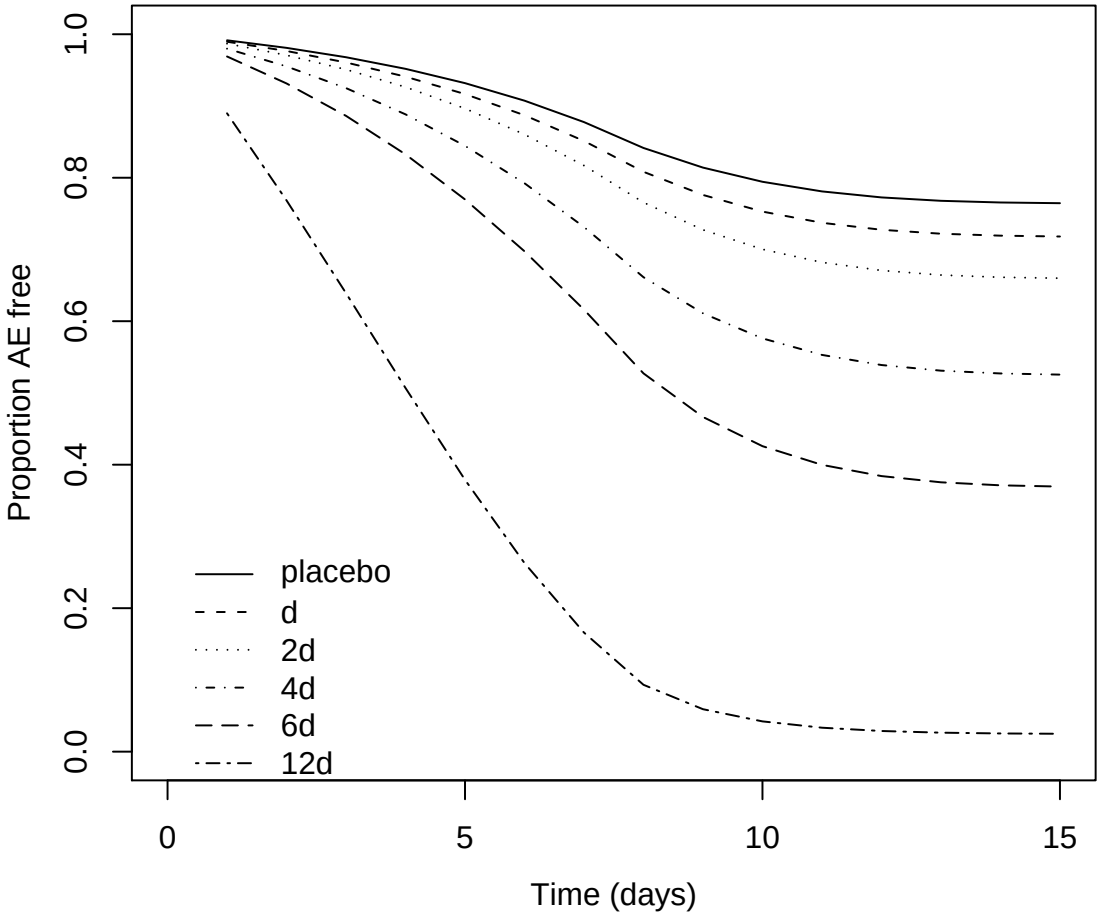

Figure 4: Survivor curves predicted by Model 15 as a function of time and dose.

dose dependency as well as changes over time. Although a formal pharmacokinetic model was not used, qualitative knowledge about the pharmacokinetic and pharmacodynamic behaviour of the compound was incorporated in the model. Given the mechanism of action of the drug, a fully mechanistic PK/PD model would imply the use of indirect response models.[2] The modeling strategy presented here offers a compromise between a highly complex and time consuming, mechanistic PK/PD-modeling approach and a less informative, purely empirical approach. Usually a fully mechanistic PK/PD-modeling approach is a challenging task due to the statistical complexity, lack of enough data or time constraints. Depending on the objectives of the modeling excercise, a simpler model can be useful. This is especially the case in the context of clinical trial simulation. It has been recognized that in rich data sets the time course of a pharmacodynamic parameter may contain enough information on the kinetics of the system to built a sensible simulation model.[4] In the application of modeling and simulation in the design of clinical trials, finding a balance between model realism and feasibility is an important challenge.

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