Interpretation of depot risperidone concentration vs. time data using a piecewise polynomial regression model

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Summary

RISPERDAL® CONSTA® (risperidone) was the first long-acting depot formulation of an atypical antipsychotic, belonging nowadays to standard treatments for schizophrenia. The microsphere technology of this depot formulation results in complex pharmacokinetics, with a delay (lag time) of peak drug levels of up to 3 to 4 weeks, and therefore it initially requires additional oral doses. We used a piecewise polynomial regression approach based on sign functions to define the complex concentration vs. time curve after a single intramuscular injection of depot risperidone. A 3-phase linear model with a logarithmic transformation of concentration data was suited to fit the concentration time data and produced valuable information on both the half-life and phase borders (deflection points).

depot formulation/microsphere galenics/pharmacokinetics/piecewise multiphase model

INTRODUCTION

Piecewise polynomial regression allows to model an effect (y, dependent, response) vs. predictor (independent, X) variable relation which underlies different physical principles [1]. Such an approach is an advantage when the underlying environmental system factors change completely. For example, the anomaly of water is based on three physicochemically different phase states: ice, fluid and gas, which are defined by separate volume–temperature models. Similarly, mood vs. time data in healthy states cannot be intermingled with mood vs. time data in depressive episodes, as the biological system factors and their relations – diurnal variation on the one hand and deep depression on the other hand – are based on different principles. Piecewise regression allows to investigate relations between variables within separate sections that share comparable underlying neurobiological conditions.

In general, pharmacokinetic models are based on differential equations, e.g. the famous Bateman equation. With some modifications, such as lag times or saturation processes, these models are suited to model almost all effect or concentrations vs. time curves and allow analytical solutions with functional associations between response variables and predictor variables [2]. The RISPERDAL® CONSTA® formulation of risperidone is a microsphere galenic formulation which delivers the drug in relevant amounts about 3 weeks after injection of the depot formulation – oral administration must be continued during this period. This specific depot ga-

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lenics was necessary as the mother compound does not have a suitable side chain to allow classical bonds of typical formulations, such as decanoate or palmitate, to form [3,4]. The physicochemical system factors are different during the first 3 weeks and during the drug liberation phase after weeks 4 and 5. Therefore, a piecewise polynomial regression model may be an alternative multiphase pharmacokinetic approach, and the aim of this study was to test this hypothesis.

METHOD

Piecewise regression: theoretical background

As outlined above, the method combines several functional relations into one composed model [5]. In mathematical terms, a simple linear-linear-linear model can be written as follows:

$$Y(x) = A + BX + C(X-D)SIGN(X-D) + E(X-F)SIGN(X-F)$$

Three different linear equations are fitted to a specific section of the predictor variable where section borders on the abscissa are specified by $SIGN(x-d)$ and $SIGN(x-f)$. The SIGN function defines the specific functional relation with optimal x-values:

$$Y = a_1 + b_1 \times X \qquad \text{if } x \le d$$
$$Y = a_2 + b_2 \times X \qquad \text{if } d < x \le f$$
$$Y = a_3 + b_3 \times X \qquad \text{if } x > f$$

The model also fits the parameters d and f, and so it provides information about a change of phases ("deflection points"). Regression sections may be adjusted by means of suitable transformations. Of course, different equations, including non-linear equations, can be inserted to optimize physiological models. However, a linear regressions with a logarithmic transformation of the Y-variable proved to be adequate for the purpose of this primary analysis: $Y' = \ln(Y) = \ln(a + b \times X)$, i.e. the inverse function leads to the illustrative exponential associations we are accustomed to from pharmacokinetics: $Y = \exp(Y') = \exp(\ln Y) = \exp(a) \times \exp(\times X)$ or $Y = K \times \exp(b \times X)$. With regard to the fitted section, the constant K may be interpreted as "Co" and b may be interpreted as the rate constant, which allows us to estimate the half-life ($T_{1/2} = \ln 2/k$) of absorption and elimination [2].

Example of piecewise modelling concentration-time data of depot risperidone

The concentration vs. time curve was simulated from published data drawn from the results of 16 volunteers who received one single dose of 50 mg intramuscular risperidone [6]. In addition, to obtain realistic clinical data, doubled retrospective drug monitoring data of schizophrenic patients who were treated with 25 mg risperidone (deltoid injection) without concomitant oral administration have been considered. All calculations were performed with commercially available statistical software (NCSS 2007, version 07.1.21, Kaysville, Utah, USA).

The model provided perfectly acceptable goodness of fit with an overall $R^2 = 0.86$ (i.e. 86% of the variation can be explained by the model). The curve fit of logarithmic concentration data is given in Figure 1. In detail, the following model parameters were estimated: a1=0.94, a2=–0.22 and a3=9.40 ng/ml. The corresponding "rate constants" were b1=0.031, b2=0.091 and b3=–0.15 per day^{-1}. The interval borders ("corners", i.e. deflection points of the model) for the different fitting regions were added up to 20.0 (d) and 39.8 (f) days.

Ln conc versus time polynomial three phase regression
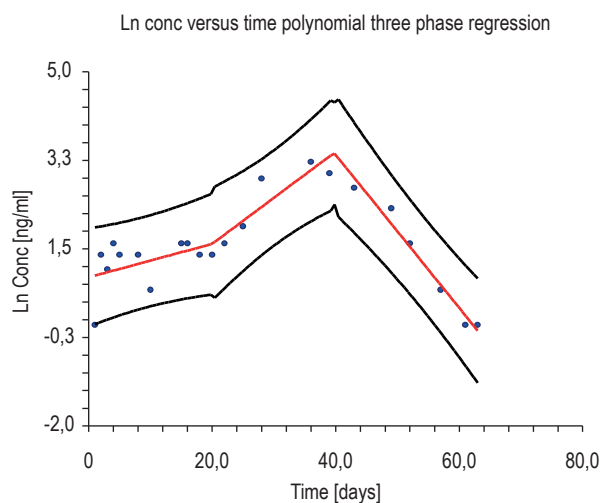
Figure 1: Linear-linear-linear piecewise regression curve including 95%-prediction limits with logarithmic [ln] transformation of the concentration data.

We may calculate the elimination half-life of the last regression section up to 4.6 days, which corresponds to a quite reasonable magnitude for

the depot formulation. The estimated absorption time (phase 2) is approximately 7.6 days, which is slightly lower compared with elimination. With regard to phase 1, the apparent absorption half-life may be calculated at 23 days (clinically there is almost no relevant change of concentration). Furthermore, we learn from the piecewise model that drug liberation actually starts after 20 days and achieves a maximum level after approximately 40 days.

DISCUSSION

The pharmacokinetics of microsphere depot formulations such as RISPERDAL® CONSTA® cannot be characterized by a single analytical pharmacokinetic solution that provides a functional concentration vs. time curve. On the contrary, the published pharmacokinetic studies use model-independent parameters such as area under the curve or maximum and minimum concentrations of the concentration vs. time curve and corresponding time points [7]. Terminal half-life of drug elimination or half-life of absorption after and before peak concentration (T_{max}) after about 32 days can be calculated using convenient approaches [6]. In contrast to these older pharmacokinetic models, the 3-phase polynomial piecewise regression model with a logarithmic transformation of the concentration data allows us to describe the whole concentration vs. time curve of a microsphere depot formulation after a single intramuscular injection.

Based on the sign function, this method defines a quasi-analytical functional association between concentration and time for risperidone. The procedure provides additional information about the deflection points of the different phases, i.e. the time points when underlying phys-

icochemical principles of drug release change. This new approach may be therefore a suitable multiphase pharmacokinetic approach for complex drug release systems such as microsphere formulations.

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