Commun Nonlinear Sci Numer Simulat 22 (2015) 451–471

Contents lists available at ScienceDirect

Commun Nonlinear Sci Numer Simulat

journal homepage: www.elsevier.com/locate/cnsns

Fractional model for pharmacokinetics of high dose methotrexate in children with acute lymphoblastic leukaemia

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ARTICLE INFO

Article history:
Received 19 April 2014
Received in revised form 25 July 2014
Accepted 16 August 2014
Available online 27 August 2014

Keywords:
Fractional model
Methotrexate pharmacokinetics
Children
Leukaemia

ABSTRACT

The aim of this study is to promote a model based on the fractional differential calculus related to the pharmacokinetic individualization of high dose methotrexate treatment in children with acute lymphoblastic leukaemia, especially in high risk patients.

We applied two-compartment fractional model on 8 selected cases with the largest number (4–19) of measured concentrations, among 43 pediatric patients received 24-h methotrexate 2–5 g/m^2 infusions. The plasma concentrations were determined by fluorescence polarization immunoassay. Our mathematical procedure, designed by combining Post's and Newton's method, was coded in Mathematica 8.0 and performed on Fujicu Celsius M470-2 PC.

Experimental data show that most of the measured values of methotrexate were in decreasing order. However, in certain treatments local maximums were detected. On the other hand, integer order compartmental models do not give values which fit well with the observed data. By the use of our model, we obtained better results, since it gives more accurate behavior of the transmission, as well as the local maximums which were recognized in methotrexate monitoring. It follows from our method that an additional test with a small methotrexate dose can be suggested for the fractional system parameter identification and the prediction of a possible pattern with a full dose in the case of high risk patients.

A special feature of the fractional model is that it can also recognize and better fit an observed non-monotonic behavior. A new parameter determination procedure can be successfully used.

1. Introduction and background

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children [1–3]. The breakthroughs in diagnostics, therapy and improvements to therapy protocols have all led to long-term curing, with an overall five-year survival rate of almost 80% in children with ALL [4–7].

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http://dx.doi.org/10.1016/j.cnsns.2014.08.014
1007-5704/

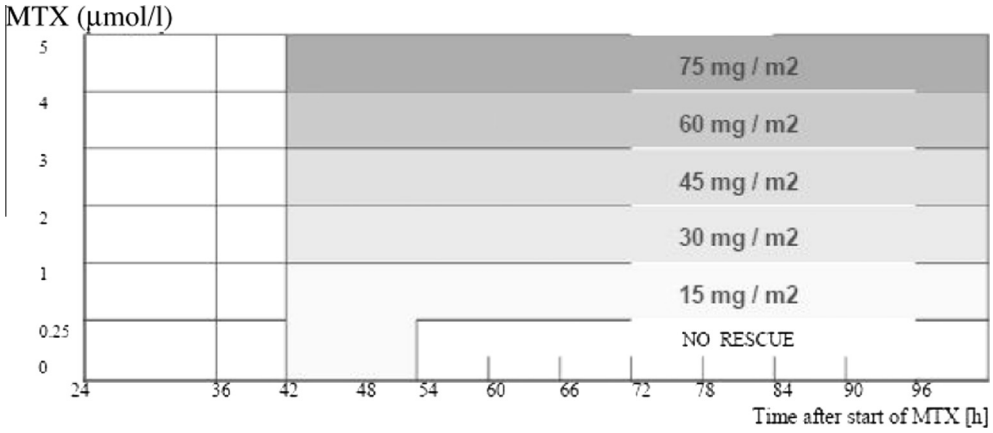

Fig. 1. Diagram for leucovorine dosage by MTX level.

Methotrexate (MTX), a folic acid antagonist and the most commonly used antimetabolite in cancer therapy, has three features that contribute to its distinguished position in cancer chemotherapy: 1. It is the only cytostatic drug that has an antidote in clinical use (leucovorine); 2. It has the widest dose-range: 3–33,600 mg/m^2; 3. It is the only anti-cancer drug where serum concentrations are monitored routinely [1–3]. Since the cytotoxic effects of MTX can be antagonized by activated folic acid (leucovorine), in the MTX therapy it is possible to include escalating dosages, unlike in case of other antineoplastics [8–10].

The intravenous (IV) application of high dose MTX (HDMTX) 5 mg/m^2/24 h infusions, achieves effective therapeutic concentrations, i.e. MTX concentrations in a steady state of 1×10^{-6} mol/l [1]. A change in the dosage or duration of HDMTX infusion is the focus of the strategy for overcoming individual differences in MTX accumulation [9], since the cytotoxic effect of MTX depends on the concentration and the length of the exposure to the drug [6–9]. The most commonly described side-effects of the MTX therapy are myelosuppression acute liver toxicity, nephrotoxicity, mucositis, and neurotoxicity [6,7,11–14]. Definitions of medical terms used in this paper are given in Appendix A.

When HDMTX infusions are applied, therapeutic drug monitoring is a standard practice for guidelines related to leucovorine rescue, especially with patients with confirmed MTX clearance or other risks related to prolonged cytotoxic concentrations (kidney or liver damage, liquid collection) [15,16].

Traditionally, the therapy protocols for ALL patients defined the risk groups according to age, sex and the leucocytes number. Today's risk evaluation includes also the characteristics of leukaemic blasts, obtained by immunophenotypic, cytogenetics and molecular diagnoses [9,10,17].

However, other factors are also known to contribute to a great variability in MTX accumulation: fertility, molecular subtype, folate cycle expression genome [5]. The association between low urine pH and high risk MTX concentrations has been well documented [18]. A standard fixed MTX dose introduced up to 7-fold spread in the range of drug concentrations in different patients with same urine pH [18]. It has also been reported that renal and hepatic function affects MTX pharmacokinetics [18]. MTX is eliminated by renal excretion. Elimination of MTX was prolonged in patients with renal impairment. MTX was metabolized to less active metabolite by the liver. Liver dysfunction could lead to impaired MTX metabolism. Then, the kidney and liver functions would be considered in the patients with reduced elimination [19].

Previous published MTX concentrations in children with ALL after infusion of HDMTX [1,18–24] revealed not only great variations in different therapy courses, but also not always decreasing order [19,20] that can hardly be predicted by classical pharmacokinetic models. For example, a nonmonotonic behavior of MTX concentrations in previously published studies is visibly evident: Min et al. on Fig. 3 [19] and Piard et al. on Fig. 4 [20]. Instead, fractional order pharmacokinetic models have proved to be better suited to represent the time-course of anomalous concentration data [25–37].

Introduction of fractional order approach in pharmacokinetics is evident from previous papers [25–32,34–37]. Application of such methods on drugs with increased variability, irregular, novel or anomalous uptake or clearance [25,26], small therapeutic range, or in patients with renal and hepatic disease [35], congestive heart failure, in newborn infants [35] and geriatric patients, is of great concern [35–37]. Beside pharmacokinetics, collections of such applications can also be found in other various biomedical interdisciplinary fields [33,38–54]. With respect to system identification using fractional models in diffusive phenomena we refer to [55] and the references therein.

The objective of the present work is introduction of fractional derivatives in pharmacokinetic analysis of MTX concentrations, in children with ALL, especially in cases of unusual kinetic behavior and high risk patients.