European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 117–130

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

PBPK model of methotrexate in cerebrospinal fluid ventricles using a combined microdialysis and MRI acquisition

Nolwenn Brandhonneur [a,b], Fanny Noury [a,c,1], Arnaud Bruyère [a,b,1], Hervé Saint-Jalmes [a,c,d], Pascal Le Corre [a,b,e,*]

[a] Université de Rennes 1, Rennes, France
[b] Laboratoire de Pharmacie Galénique, Biopharmacie et Pharmacie Clinique, IRSET U1085, Rennes, France
[c] LTSI, INSERM, UMR 1099, Rennes, France
[d] CRLCC, Centre Eugène Marquis, Rennes, France
[e] Pôle Pharmacie, CHU de Rennes, France

ARTICLE INFO

Article history:
Received 5 November 2015
Revised 8 March 2016
Accepted in revised form 18 April 2016
Available online 30 April 2016

Keywords:
Methotrexate
CSF ventricle administration
Gd-DOTA
MRI
PBPK modeling

ABSTRACT

The objective of the study was to evaluate the distribution of methotrexate (MTX) in cerebrospinal fluid (CSF) lateral ventricles and in cisterna magna after 3rd intraventricular CSF administration in a rabbit model.

MTX or gadolinium chelate (Gd-DOTA) was administered in the 3rd ventricle with a local microdialysis to study the pharmacokinetics at the site of administration and with a simultaneous magnetic resonance imaging (MRI) acquisition in the 3rd ventricle, the lateral ventricles and in the cisterna magna. A specific CSF Physiologically Based Pharmacokinetic (PBPK) model was then extrapolated for MTX from Gd-DOTA data.

The relative contribution of elimination and distribution processes to the overall disposition of MTX and Gd-DOTA in the 3rd ventricle was similar (i.e., around 60% for CLE and 40% for CLI) suggesting that Gd-DOTA was a suitable surrogate marker for MTX disposition in ventricular CSF. The PBPK predictions for MTX both in CSF of the 3rd ventricle and in plasma were in accordance with the *in vivo* results.

The present study showed that the combination of local CSF microdialysis with MRI acquisition of the brain ventricles and a PBPK model could be a useful methodology to estimate the drug diffusion within CSF ventricles after direct brain CSF administration. Such a methodology would be of interest to clinicians for a rationale determination and optimization of drug dosing parameters in the treatment of leptomeningeal metastases.

1. Introduction

The meninges are a unique site of recurrence of malignancies as a result of a rather limited penetration of systemically administered anticancer drugs through the blood–brain barrier.

In association with systemic chemotherapy or radiotherapy, direct CSF administration of anticancer drugs, either via intrathecal or via intraventricular route, has proved to be an effective strategy for the prevention and the primary treatment of leptomeningeal leukemia's and lymphomas while leptomeningeal metastases from solid tumors usually respond less to intrathecal chemotherapy [1–3].

Currently, only MTX and cytarabine are routinely used intrathecally, and most of the times in association with hydrocortisone. These cell-cycle specific drugs, acting during the S phase of the cell-cycle, are most effective if drug concentrations are maintained for a long period of time. This requires either repeated intrathecal administration via lumbar punctures or a neurosurgical placement of an indwelling ventricular access device (i.e., Ommaya reservoir).

Continuous administration of 10 mg MTX for five consecutive days in a lateral ventricle via a subcutaneous port has led to

Abbreviations: CSF, cerebrospinal fluid; MTX, methotrexate; PET, positron emission tomography; PBPK, Physiologically Based Pharmacokinetics; MRI, magnetic resonance imaging; IM, intramuscular administration; IV, intravenous administration; Gd-DOTA, gadolinium chelate; AUC, area under curve; CLE, elimination clearance; CLI, intercompartmental distribution clearance; RVT, rich-vascularized tissue; PVT, poor-vascularized tissue; RL, relative loss of microdialysis internal standard; RR, relative recovery of analyte.

* Corresponding author at: Laboratoire de Pharmacie Galénique, Biopharmacie et Pharmacie Clinique, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Rennes 1, 35043 Rennes Cedex, France.
E-mail address: pascal.le-corre@univ-rennes1.fr (P. Le Corre).
[1] These authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.ejpb.2016.04.012
0939-6411/

concentrations exceeding the therapeutic levels of 10^{-6} M with reduced complications [4].

Alternatively, a slow-release formulation of cytarabine as multivesicular particles leads to a prolonged exposure (elimination half-life around 50–60 h), approximately forty-times longer than standard cytarabine [5]. Although such a formulation has a pharmacokinetic advantage over the standard formulation as a result of a reduced frequency and total number of administrations, severe neurologic events have been described [6].

Beside these two routinely used drugs, in order to improve the management of neoplastic meningitis, several anticancer agents have been studied in animal models: topotecan [7] and karenitecin, a lipophilic camptothecin [8], gemcitabine in nonhuman primates [9,10] and pemetrexed in rats [11].

Phase I clinical trials have been performed especially in children showing that topotecan [12] and busulfan [13] are rather well tolerated and are promising newer agents for treatment of leptomeningeal disease. However, gemcitabine that has preclinical and clinical activities against a wide variety of solid tumors as well as leukemia's and lymphomas, has been shown to have a potential for severe neurotoxicity in adults [14]. In central nervous system, dissemination of non-Hodgkin's lymphoma is a significant cause of morbidity and death. A phase I study of the anti-CD20 monoclonal antibody rituximab given as monotherapy via intraventricular route (10–50 mg) showed encouraging results and suggested the association with methotrexate [15]. However, in a clinical series of patients, association of rituximab with liposomal aracytine in recurrent lymphomatous meningitis has led to a modest palliative activity [16].

As new drugs have not yet improved significantly the outcome of neoplastic meningitis, optimization of the route of administration has been studied. Recently, preclinical studies in a piglet model have shown that continuous administration directly in the 4th ventricle would have a potential pharmacokinetic advantage over lumbar or lateral ventricular administration [17,18]. Etoposide (2.5 mg) and MTX (2 mg) administration on five consecutive days did not lead clinical or radiographic evidence of damage with much higher concentrations in the 4th ventricle than in the lumbar cistern.

It is clear that concurrent research on new drug candidates for intrathecal therapy and improvement on intrathecal administration are needed to optimize the management of neoplastic meningitis. However, there is a critical factor that has not been yet clearly addressed and that deserves much attention. This factor is the 3-Dimensional (3D) biodistribution of the drugs within the cerebral CSF in order to make sure that therapeutic unbound drug concentrations are obtained at cancer cells. Indeed, drug efficacy of this local chemotherapy may be impeded by an uneven distribution. Hence, the knowledge of drug concentration in different parts of these spaces is of paramount interest for a rationale determination and the optimization of the parameters of drug dosing (dose, concentration, volume and speed of injection, additional drugs to modify MTX clearance such as transporter inhibitors).

Several authors have studied with the pharmacokinetics of anticancer agents injected intrathecally either after intraventricular (lateral ventricle or 4th ventricle) or lumbar administration with a majority of studies performed with MTX either in humans [19,20] or in a nonhuman primates model allowing the description of the neural tissue distribution [21–23].

If the CSF distribution of drugs along the neuraxis is quite well documented, this is not the case for the distribution within the brain ventricles. Such point is of crucial significance since anticancer drugs administrated via a ventricle have to diffuse within cerebral CSF to reach cancer cells.

To study the 3D drug distribution, positron emission tomography (PET) after intraventricular administration would be an interesting method. PET studies with the administration of a carbon-11-labeled (11C) or fluorine-18-labeled (18F) drug candidate allow describing the drug concentration–time profile in body spaces targeted for the treatment. 18F is the most attractive PET radioisotope allowing for imaging durations of up to ten hours. However, a significant drawback stems from the fact that drug molecules contain fluorine in their native structure are rare. Hence, despite its rather short half-life (around 20 min), the majority of PET studies are performed with 11C drug molecules. Furthermore, particular challenges in the synthesis of PET radiotracers include time constraints due to the short radioactive half-lives of the radioisotopes, the need for automatization of procedures to protect from radiation exposure and the necessity to produce a radiotracer which meets the quality criteria of a drug for intrathecal injection into humans. For those reasons PET studies may not be the ideal approach.

Magnetic resonance imaging (MRI) is a noninvasive technique providing high-resolution anatomical information with excellent soft tissues contrast, and the ability to reconstruct a 3D representation of a volume of interest. Gadolinium-enhanced MRI further increases the contrast on T_1-weighted MR images of anatomical regions of interest. From these images, it is possible to calculate the relative concentration of gadolinium in the tissue of interest as a function of time. Microdialysis is particularly relevant to study the disposition of drugs because it allows sampling in biological spaces without altering the local hydrodynamics that could interfere with the disposition of the drug. This is particularly relevant for CSF that has a low flow instead of blood. This technique measures unbound concentrations, and has found significant applications in pharmacokinetics in animals but also in humans [24–26].

The aim of the study was to evaluate the distribution of methotrexate (MTX) in cerebrospinal fluid (CSF) lateral ventricles and in cisterna magna after 3rd intraventricular CSF administration in a rabbit model. For that purpose we used a combination of CSF intraventricular microdialysis with MRI after administration of a contrast agent in a ventricle which would allow a quantitative evaluation of the 3D drug distribution in CSF. Indeed, microdialysis allows the determination of the absolute concentration of a drug (i.e., a contrast agent) as a function of time in a specific area while MRI allows 3D determination of its relative concentration as a function of time.

To gain further insight into the CSF ventricular distribution of MTX we set up a rabbit model with administration of Gd-DOTA as a surrogate marker for MTX and microdialysis in the 3rd ventricle with concurrent brain MRI acquisition in different areas of the cerebral CSF to generate CSF gadolinium concentrations in the 3rd ventricle, lateral ventricles and magna cisterna.

MTX pharmacokinetics was studied using the same animal model after 3rd intraventricular administration and compared with intralumbar administration and a CSF PBPK model was developed to estimate MTX distribution in the CSF of the different cerebral ventricles.

2. Materials and methods

2.1. Chemicals

Methotrexate (MTX – Mylan, France) and gadolinium chelate (Gd-DOTA – gadoteric acid: Dotarem, Guerbet, France) were used as the substance of interest and theophylline (Sigma, France) as an internal standard of the microdialysis technique. All reagents were of analytical grade.

2.2. In vivo study design

2.2.1. Animals

The study was performed according to a protocol approved by the Local Committee of Laboratory Investigation and Animal Care