Effect of probenecid on ventricular cerebrospinal fluid methotrexate pharmacokinetics after intralumbar administration in nonhuman primates

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Abstract Purpose: Intrathecal methotrexate (MTX) achieves high concentrations in the cerebrospinal fluid (CSF) following intralumbar administration. However, peak ventricular CSF MTX concentrations are highly variable and are <10% of those achieved with intraventricular dosing. The objectives of this study were to evaluate the effect of intralumbar and intravenous probenecid on ventricular CSF MTX concentrations after intralumbar administration of MTX, and to compare the pharmacokinetics of MTX after intralumbar and intraventricular administration.

Methods: Nonhuman primates (Macaca mulatta) with permanently implanted catheters in the lateral and fourth ventricles received 0.5 mg intraventricular (lateral ventricle) MTX, or 0.5 mg intralumbar MTX with and without intralumbar or intravenous probenecid. Animals were kept prone for 1 h after MTX administration, and ventricular CSF was sampled up to 48 h from a fourth ventricular Ommaya reservoir. MTX concentrations were measured using the dihydrofolate reductase enzyme inhibition assay. Area under the ventricular CSF MTX concentration-time curve (AUC) was used as a measure of MTX exposure.

Results: Peak ventricular CSF MTX concentrations and AUCs were highly variable after intralumbar MTX administration. Ventricular CSF MTX AUCs increased by a mean of 3.2-fold after the addition of intralumbar probenecid. Intravenous administration of probenecid did not result in an increase in ventricular CSF MTX AUCs. Asymptomatic pleocytosis was observed in all animals after intralumbar probenecid administration. Ventricular CSF MTX concentrations and AUCs were less variable after intraventricular administration of MTX.

Conclusion: The administration of intralumbar but not intravenous probenecid increases the ventricular CSF MTX exposure after intralumbar MTX administration.

Keywords Methotrexate · Cerebrospinal fluid · Intrathecal · Probenecid · Nonhuman primate model · Pharmacokinetics

Abbreviations AUC: area under the concentration-time curve · CSF: cerebrospinal fluid · CNS: central nervous system · i.t.: intrathecal · i.v.: intravenous · MTX: methotrexate

Introduction

Intrathecal (i.t.) methotrexate (MTX) is a cornerstone of prevention and treatment of leptomeningeal leukemia. Because of the small volume of cerebrospinal fluid (CSF), MTX concentrations exceeding 100 µM can be achieved with a dose of 12 mg i.t., resulting in a substantial pharmacokinetic advantage for this route of administration [5, 16, 18]. MTX administered i.t. will induce a remission in 80% to 90% of children with acute lymphoblastic leukemia who experience a meningeal relapse, but few of these patients are cured with i.t. therapy alone [1]. As adjuvant or preventive therapy in children with newly diagnosed acute lymphoblastic leukemia, i.t. MTX alone or in combination with i.t. cytarabine or cranial radiation significantly reduces the meningeal relapse rate [13].

A major limitation of i.t. drug administration is nonuniform distribution of drug throughout the subarachnoid space. Ventricular CSF MTX concentrations after an i.t. dose are <10% of the...
concentrations achieved with an intraventricular dose and have a high interpatient variability. After intralumbar injection of 6.25 or 12.5 mg/m² in humans, peak ventricular CSF MTX concentrations range from 0.6 to 22 µM, which is substantially lower than the 200 µM peak concentration achieved after intraventricular administration of 6.25 mg/m² [18]. Lower CSF MTX concentrations at sites distant from the site of injection substantially reduce the pharmacokinetic advantage and efficacy of i.t. MTX. The MTX concentration within the CSF after i.t. administration is dependent on the site and mode of administration [2], body position after an intralumbar dose [3], bulk CSF flow and absorption, choroidal drug uptake and clearance, and diffusion or transport of drug across the CSF-brain interface [4].

Surgically implanted ventricular access devices, such as the Ommaya reservoir, were developed to provide a convenient and reliable route for delivering drugs directly into the ventricular CSF [15]. Although there are no large, prospective comparative trials testing the efficacy of this route of administration, retrospective studies suggest that the use of these devices is more efficacious and less toxic than the traditional intralumbar route [6, 7, 12]. In addition, intraventricular MTX injection achieves higher and less-variable drug concentrations in the ventricular CSF and better distribution of drug throughout the subarachnoid space [18].

MTX is a weak acid, and probenecid can inhibit renal tubular transport of MTX [9]. A probenecid-sensitive transport pump is also present in the choroid plexus of rabbits [19]. In rabbits, intraperitoneal or intraventricular administration of probenecid concurrently with i.t. MTX has been shown to result in higher MTX CSF concentrations, slower clearance of MTX from the CSF, and lower plasma MTX concentrations [10, 17, 19]. In humans, oral probenecid (1.7 g/m²) increases CSF MTX concentrations 2.8- to 4.2-fold after systemic administration of high-dose MTX [11], and at a dose of 2.5 g/m² probenecid prolongs the terminal half-life of MTX in CSF after intraventricular MTX administration [8]. Intraventricular probenecid administered concurrently with intraventricular MTX enhances MTX distribution to the lumbar space in Rhesus monkeys, suggesting that the probenecid-sensitive transport system may be widely distributed in the meninges [2].

The present study, which was performed in nonhuman primates, was designed to assess (1) the effect of concurrent intralumbar probenecid on the ventricular CSF distribution of intralumbar MTX, (2) the toxicities of i.t. administered probenecid, (3) the effect of intravenous (i.v.) probenecid on the ventricular CSF distribution of intralumbar MTX, and (4) the interanimal variability of ventricular CSF MTX exposure after intralumbar and intraventricular MTX administration.

Materials and methods

Drugs and chemicals

MTX without preservative and leucovorin were obtained from Immunex (Seattle, Wash.). Dihydrofolate reductase was obtained from Biopure Corporation (Cambridge, Mass.). Probenecid and other chemicals used in preparation of drug and for the dihydrofolate reductase inhibition assay were obtained from Sigma Chemical Co. (St. Louis, Mo.).

Animals

Six adult Rhesus monkeys (Macaca mulatta), each with an indwelling lateral ventricular catheter attached to a subcutaneous access port for drug administration and a fourth ventricular catheter attached to an Ommaya reservoir for CSF sampling as previously described [14], were used in this study (Fig. 1). MTX was administered via direct intralumbar injection in four animals, and through a lumbar catheter attached to a subcutaneous access port in two animals (R383A and R395). The monkeys ranged in weight from 9.4 to 12.1 kg. They were fed Purina Monkey Chow twice daily and were group-housed in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, National Academy Press, Washington DC, 1996).

Experiments

When administered alone by the intralumbar or intraventricular route, MTX was diluted in 0.9% sodium chloride to a final concentration of 0.5 mg/ml. When administered via the intralumbar route in combination with probenecid, MTX and probenecid were solubilized in 0.1 N NaOH, and the pH was adjusted to 7.5–8.5 with 1 N HCl, to give a final concentration of 0.5 mg MTX/ml and 5 or 24 mg probenecid/ml. For i.v. administration, probenecid was

![Fig 1 Diagram of nonhuman primate model. CSF samples were obtained from the fourth ventricular catheter that is attached to a subcutaneous Ommaya reservoir. MTX was administered into the lumbar space via intralumbar injection or intraventricularly through the access port that is attached to the lateral ventricular catheter](image-url)