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Original Research

Flow Rate and Apparent Volume of Cerebrospinal Fluid in Rhesus Macaques (*Macaca mulatta*) Based on the Pharmacokinetics of Intrathecally Administered Inulin

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Cerebrospinal fluid (CSF) flow rate and volume are fundamental to the design and interpretation of preclinical pharmacokinetics and pharmacodynamics studies in NHP. To determine the values of CSF flow rate and volume, we evaluated the plasma and CSF pharmacokinetics of inulin, an inert polysaccharide tracer, in 5 rhesus macaques with CSF ventricular reservoirs and lumbar ports; these reservoirs and ports facilitate humane intrathecal administration and serial CSF sampling in unanesthetized macaques. Inulin was administered intrathecally via the CSF ventricular reservoir (n = 3), followed by the collection of lumbar CSF via the lumbar port and plasma. The contribution of dietary inulin was evaluated by using pre- and postprandial inulin plasma concentrations (n = 2) and a feed analysis of the NHP diet. Inulin concentrations were quantified using ELISA. Pharmacokinetic parameters were calculated by using noncompartmental methods. Daily diet was analyzed for inulin by using Official Method no. 997.08 of AOAC International. In male rhesus macaques, the mean CSF flow rate, established via inulin clearance after IT administration, was 0.018 ± 0.003 mL/min; mean CSF volume, established based on apparent volume of distribution, was 10.17 ± 0.63 mL. In plasma, inulin was quantifiable in all pre-administration samples and increased over the sampling period, precluding interpretation of plasma pharmacokinetics. Evaluation of the effect of diet on plasma concentrations established quantifiable inulin levels that showed minimal variation relative to the prandial state. Analysis of the feed detected 5 inulin types ranging from 1100 to 1440 mg per100 g. The diet was the source of detectable pre-administration inulin plasma concentrations, whereas inulin was not detected in CSF before inulin administration.

Abbreviations: AUC, Area Under the Curve, BBB, blood–brain barrier; CSF, cerebrospinal fluid; IT, intrathecal, $K_{el,}$ elimination rate; V_d, volume of distribution

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Successful treatment of CNS disease with a therapeutic agent requires CNS penetration of the agent across the blood–brain barrier (BBB) to its site of action, to achieve an effective concentration and duration.[30] The BBB[7] limits access into the CNS for systemically administered agents through a complex physical and chemical system.[28] In the presence of CNS disease such as malignant glioma, the properties of the BBB may undergo changes permitting greater diffusion of systemically administered agents into the CNS.[28] However, the BBB is not static, and permeability changes in the presence of disease may be transient, occur only partially, or not occur.[30] Therefore, an agent's activity against a target demonstrated in vitro, or in vivo in preclinical murine animal models, may be ineffective in patient clinical trials, when the agent fails to reach the target or does not reach the target at an effective concentration or duration[17,27] due to the varying, potentially restrictive, permeability of the BBB in patients. Intrathecal (IT) drug administration is an established alternative administration route that bypasses the BBB and delivers the agent directly into the CSF.[29] IT administration is accomplished as intraventricular delivery into the ventricles of the brain or as intralumbar delivery into the spinal column.

Efficacious treatment regimens for systemic or IT administration of an agent fundamentally rely on preclinical pharmacokinetics–pharmacodynamics studies that provide information on parameters such as drug plasma and CSF concentrations, duration of measurable drug (pharmacokinetics) or drug activity (pharmacodynamics), drug elimination and distribution, and adverse events.[22,26] Drug exposure, or concentration of a drug over time, is defined by the Area Under the Curve, (AUC). The duration is typically described as the elimination half-life ($t_{1/2}$), which is the time required for half of the agent to be biologically reduced quantitatively. Elimination is represented by clearance, which is defined as the rate at which an agent is biologically

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removed. Distribution, as the apparent volume of distribution (V_d), is the apparent fluid volume required to contain the total amount of drug administered as it relates to the drug concentration in the biologic fluid (plasma, serum, whole blood, or CSF) from which it was measured.[1]

The interpretation of pharmacokinetics parameters, such as AUC, $t_{1/2}$, clearance, and V_d, to develop IT treatment rationales is improved when the species-specific values of CSF flow rate and volume are available for comparison to preclinical pharmacokinetics study results. Uniquely, the values of CSF volume and flow rate are independent of body weight,[11] and they serve to establish the potential concentration of drug in the CSF space (exposure and duration) and a mechanism for clearance via either CSF flow or absorption (elimination and distribution).

Previously established NHP CSF access models—the CSF ventricular reservoir[12] and lumbar port[16] models (Figure 1)—were developed in combination and used with inulin to evaluate rhesus macaque CSF flow rate and volume. These NHP models, developed in our laboratory, facilitate humane systemic and IT administration (via the CSF ventricular reservoir for the current study) as well as rapid serial CSF collection (via the lumbar port) and plasma collection, via an indwelling femoral intravenous port, in unanesthetized rhesus macaques. Inulin, a plant-based water-soluble polysaccharide, is relatively unaffected by absorption or secretion and is resistant to degradation allowing the substance to be used as a tracer in biologic fluid.[4,19] Because these properties of inulin preclude diffusion across the BBB and tissue absorption, a flow rate and volume can be calculated by using a known administered quantity.

In the current study, we determined the CSF flow rate via clearance and of volume via V_d (hereafter as apparent volume) in rhesus macaques after intraventricular administration of inulin, lumbar CSF collection, and the subsequent quantification and pharmacokinetics analysis of the agent in CSF. Plasma concentrations of inulin were determined also. Because inulin was found to be quantifiable in the plasma prior to intraventricular administration for the pharmacokinetics study, we performed a secondary study to analyze the daily feed as a potential source of inulin in the plasma and to determine the influence of the daily NHP diet on pre- and postprandial plasma inulin levels.

Materials and Methods

The NCI Animal Care and Use Committee approved this study. Care was provided in accordance with the National Research Council *Guide for the Care and Use of Laboratory Animals*, 8th edition:[10] where possible NHP were socially housed, and the research was conducted humanely. Five male rhesus macaques (*Macaca mulatta*; weight, 8.0 to 10.6 kg) were used in pharmacokinetic (n = 3) and dietary (n = 2) studies. All 5 macaques had previously been developed as NHP CSF access models; 3 of these animals were used in the pharmacokinetic study, and 2 were used for the dietary study and therefore underwent plasma collection without receiving intraventricular inulin administration as an experimental agent.

NHP CSF access models. Three macaques, previously developed as CSF models with ventricular reservoir and lumbar port models, were used for the inulin pharmacokinetics study. The CSF ventricular reservoir model (Figure 1) consists of an indwelling CSF ventricular catheter (located in the lateral or 4th ventricle) attached to a subcutaneous silicone CSF reservoir. In addition, these animals were developed as lumbar port models. The lumbar port model consists of an indwelling CSF lumbar catheter attached to a subcutaneous titanium port (Figure 1). The combination of these 2 models permitted intraventricular

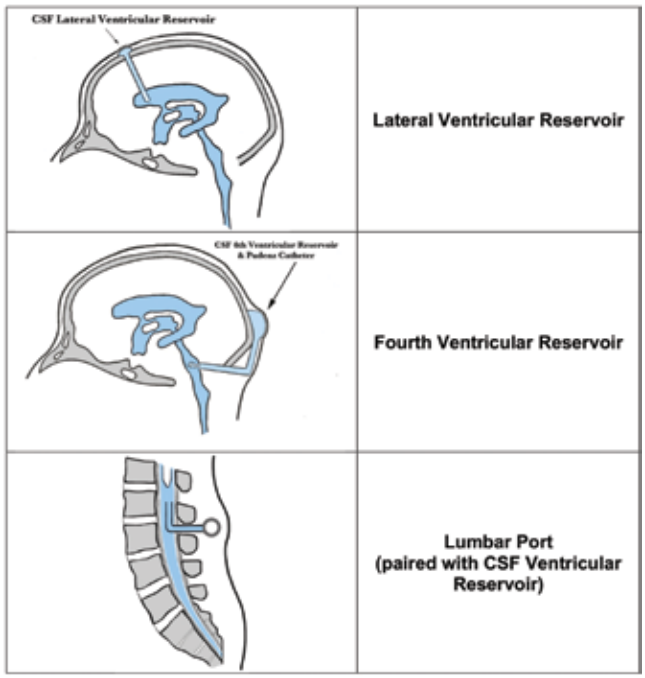

Figure 1. NHP CSF access models. CSF ventricular (lateral and 4th) reservoirs and lumbar port.

administration of inulin, via the CSF ventricular reservoir, with unbiased lumbar CSF sampling via a lumbar port positioned caudally to the CSF ventricular reservoir. In addition, the models were developed with indwelling and subcutaneous jugular and femoral intravenous ports, but for this study, only the femoral port was used for blood collection.

The macaques were recovered from any surgeries for at least 6 mo and had successfully participated in prior pharmacokinetics studies with chemotherapeutic agents after a minimal washout period of 4 wk.

Study clearance and monitoring. Macaques eligible for the study were assessed within normal limits by veterinary physical examination, neurologic assessment, and blood chemistries with complete blood counts. After administration, the animals were monitored for any change from the baseline clinical and neurologic status, determined during eligibility assessment as outlined earlier, through daily direct observation and twice-weekly clinical chemistry and CBC analyses. Monitoring began immediately after inulin administration and continued for a minimum of 2 wk.

Agents. To ensure sterility, inulin (from chicory, molecular weight of 522.453 g/mol, sterile, in saline solution, and USP grade for injection, BioPhysics Assay Laboratory, Worcester, MA) was filtered through a 0.22-µm filter (MilliporeSigma, Burlington, MA) prior to administration.

Diet.

The standard colony diet (Purina LabDiet 5045 NHP high-protein extruded biscuits, Animal Specialties Provisions, LLC, Quakertown PA), was fed twice daily to each animal in a quantity determined by veterinary assessment to be nutritionally fulfilling.

Pharmacokinetic study. *General.* Food was withheld from the macaques for 12 h prior to sedation with ketamine (10 mg/kg, Zetamine, VetOne Boise, ID). The CSF ventricular reservoir and lumbar and femoral ports were aseptically prepared with chlorhexidine and alcohol application in triplicate and patency confirmed. Pre-administration plasma, via the femoral port, and CSF samples, via the lumbar port were collected. The NHP was

recovered to a perched position and restrained via the pole and collar system,[13] for sample collection. Environmental enrichment in the form of human interaction, food treats, and videos were provided during the restraint period of 10 h. The macaques were returned to their home cage nonsedated by using a pole and collar, and fed the standard diet previously described. For the final CSF sample collection (at 24 h), food was withheld for 12 h, and macaques were sedated with ketamine, the lumbar port aseptically prepared as previously described, and lumbar CSF collected.

Dosage, routes of administration, and sampling. The inulin dose of 2 mg was used for tolerability and comparison with a previous NHP pharmacokinetics study of dexamethasone and prednisone,[2] performed in our laboratory, where inulin was used in combination with the steroid study agents during intraventricular administration. The 2-mg inulin dose provided quantifiable inulin CSF concentrations and was well tolerated in the previous study.

To avert any potential pain, the preparation for and administration of intraventricular inulin was performed while the animal was still under ketamine sedation after aseptic port preparation and prior to restraint. An equivalent volume of CSF to that of the infusion was removed from the CSF ventricular reservoir, to prepare for intraventricular administration. Via the CSF ventricular reservoir, 2 mg of sterile inulin was administered in a 0.5-mL volume as a bolus over 1 min. After intraventricular administration, the CSF ventricular reservoir was depressed and allowed to refill with CSF 4 to 10 times, prompting CSF flow and complete mixing of the agent and CSF within the ventricular space.[24,31]

Whole blood was collected from a femoral port in a volume of 3 mL into sodium heparin tubes at 0, 2, 4, 6, 8, and 10 h. The blood samples were immediately spun at 1409 x *g* for 5 min in a refrigerated centrifuge, and the resulting plasma volume was decanted into a collection vial. CSF was collected from the lumbar port in a volume of 300 µL at 0, 5, 10, 15, and 30 min and 1, 2, 3, 4, 6, 8, 10, and 24 h. The volume of CSF collected per sample was not mechanically restored by saline replacement. Plasma and CSF samples were stored at –80 °C until analysis.

Dietary study. *Feeding schedule and feed analysis.* Two schedules were used. In one, each macaque received a morning meal of Purina 5054 diet and blood was sampled 4 h later (postprandial). In the other, macaques were fasted for 18 and 22 h, and blood collected at the end of the fast, before eating (preprandial). The amount of feed was not experimentally controlled and was provided in accordance with veterinary determined dietary guidelines for each animal.

A 100-g sample of Purina LabDiet 5045 feed was collected for inulin analysis. The feed was analyzed for inulin (fructooligosaccharide) content according to Official Method no. 997.08 of AOAC International (Covance, Madison WI).

Plasma Sampling. To promote intravenous port patency by limiting usage to serial collection during pole-and-collar restraint, the macaques were sedated with ketamine, and blood was collected by percutaneous venipuncture of the femoral vein contralateral to the femoral port. Whole blood was collected in a volume of 3 mL into sodium heparin tubes. The whole-blood samples were processed and stored as described above in the section "Pharmacokinetic Study - Dosage, Routes of Administration, and Sampling."

Grading of adverse study events. All NHP used in this study had a physiologically normal clinical baseline, which was required for study eligibility. Specifically, macaques used in the study were within normal limits based on veterinary physical examination, neurologic assessment, and blood chemistries with complete blood counts.

After the administration of inulin, the animals were monitored for any change from the baseline clinical and neurologic status established during eligibility assessment. Assessment after inulin administration was performed by daily direct observation and twice-weekly clinical chemistry and CBC analyses. Monitoring began immediately after inulin administration and continued for a minimum of 2 wk. Changes were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).[21]

Pharmacokinetic sample analysis and calculation of pharmacokinetic parameters. Inulin concentrations in NHP plasma and CSF samples were quantified by using the Functional Immunoassay Technology Glomerular Filtration Rate (FIT-GFR) Kit for Inulin (BioPhysics Assay Laboratory). The lower limit of quantification is 10 ng/mL.

Values for the maximum concentration (C_{max}) and the time at which the maximum concentration occurred (T_{max}) were obtained by direct observation of data. Inulin pharmacokinetic parameters for CSF were calculated by using noncompartmental methods and Phoenix WinNonlin 6.4 software (Certara, Cary, NC).

If concentrations did not reach zero during the sampling period, AUC was determined by using the log-linear trapezoidal rule extrapolated to time infinity (i.e., $AUC_{infinity}$). $AUC_{0\text{-}infinity}$ was calculated as $AUC_{0\text{-}24} + AUC_{24\text{-}infinity}$, where $AUC_{24\text{-}infinity}$ was calculated via C_{last}/ elimination rate (K_{el}). K_{el} was determined as the slope of the line of best fit through the final 3 concentration points; t1/2 was determined as the natural log of 2 divided by K_{el}. Clearance was determined as dose divided by the $AUC_{0\text{-}infinity}$. Because the total volume of CSF is not physiologically dependent on body weight,[11] CSF clearance was not normalized to weight. V_d) was calculated as clearance divided by K_{el}.[1]

Results

The CSF pharmacokinetics values for inulin are shown in Table 1. The pharmacokinetics study involved 3 macaques that received inulin as an intraventricular bolus into the CSF ventricular reservoir and collection of lumbar CSF via the lumbar port, with plasma sampling. Data from all 3 macaques was suitable for evaluation. Inulin was quantifiable in the CSF and plasma. The CSF sample collection period was 0 to 24 h, with a mean duration of quantifiable samples for 23.9 ± 0.1 h. Individual CSF concentrations are shown in Figure 2. Intraanimal variability in inulin CSF concentrations was minimal.

The plasma sample collection period was 0 to 10 h, with a mean duration of quantifiable samples of 10 ± 0 h for all macaques. Inulin was detectable and quantifiable (range, 0.101 to 0.379 µg/mL) in the pre-dosing plasma samples from all macaques. Plasma concentrations increased over the 2- to 10-h sampling period, with moderate intraanimal variability (Figure 3). The lack of a zero plasma-inulin baseline precluded pharmacokinetics plasma analysis.

The dietary study used plasma collection from 2 macaques at preprandial timepoints of 18 and 22 h and a 4 h postprandial period. Inulin was measured in the plasma of both animals. The 18-h mean preprandial plasma inulin concentration was 0.135 ± 0.034 µg/mL (CV, 25%). The mean 22-h preprandial plasma inulin concentration was 0.146 ± 0.097 µg/mL (CV, 67%). The mean 4-h postprandial plasma inulin concentration was 0.147 ± 0.084 µg/mL (CV, 46%; Figure 4). The feed analysis of the Purina 5045 diet detected inulin with 4, 6, 10, and 25 degrees of polymerization (Table 2).

Table 1. Individual and mean inulin CSF pharmacokinetics parameters after intraventricular administration of 2 mg

Macaque	1	2	3	mean ± 1 SD	% CV
CSF Reservoir Location	Fourth	Lateral	Lateral		
C_{max} (µg/mL)	144.84	193.60	290.60	209.68 ± 74.2	35.39
T_{max} (hr)	4	4.03	2	3.34 ± 1.16	34.82
AUC_{inf} (hr*µg/mL)	2378.64	1648.91	1741.55	1923.03 ± 397.02	20.66
t1/2 (hr)	8.67	6.05	5.70	6.80 ± 1.6	23.71
clearance (ml/min)	0.014	0.020	0.019	0.018 ± 0.003	18.63
V_d (ml)	10.49	10.58	9.44	10.17 ± 0.06	6.24

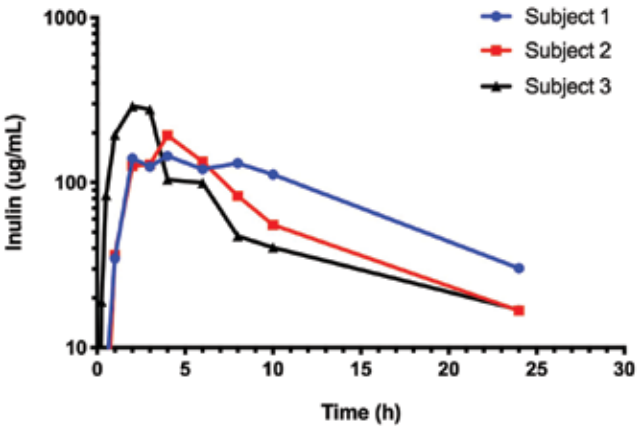

Figure 2. Individual NHP inulin CSF concentrations after intraventricular administration of 2 mg.

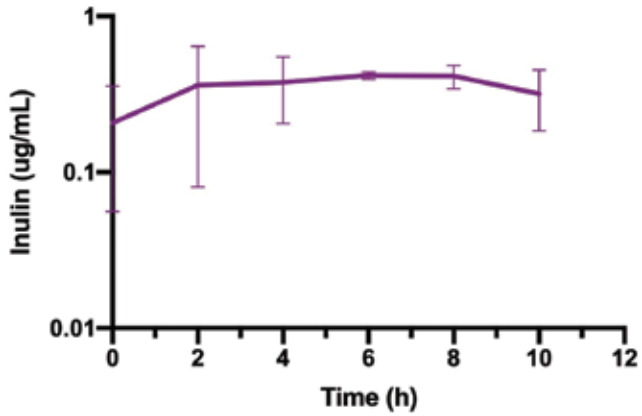

Figure 3. Mean inulin plasma concentrations after intraventricular administration of 2 mg.

Intraventricular administration of inulin was well tolerated by all macaques. No changes from the baseline physiologic and neurologic status were detected after intraventricular inulin administration. Therefore, the study has a CTCAE rating of no adverse events.

Discussion

We performed a pharmacokinetic study by using intraventricular administration of inulin, an inert biologic fluid tracer, and determined the CSF flow rate and apparent CSF volume for adult rhesus macaques based on the pharmacokinetic parameters of clearance and apparent volume of distribution.

A CSF ventricular reservoir was used for administration, and a lumbar port for CSF sampling; a mean CSF flow rate of 0.018 ± 0.003 mL/min and apparent volume of 10.17 ± 0.06 mL

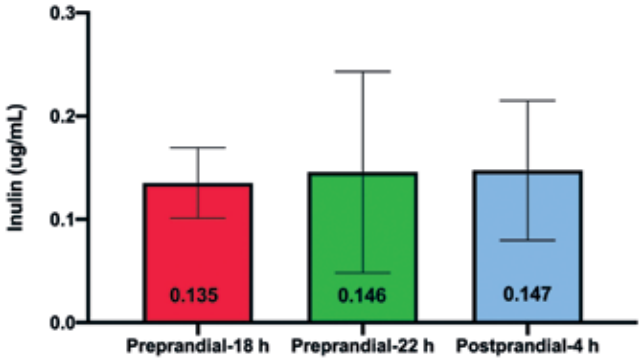

Figure 4. Mean fasting and nonfasting plasma concentrations of dietary inulin.

Table 2. Inulin Feed Analysis of the Purina LabDiet 5045 NHP High Protein Dry Biscuit Diet (Tile has been revised)

Inulin type	Amount (mg/100 g of feed)
DP10	1180
DP4 (Fn)	1130
DP4 (GFn)	1140
DP6	1290
DP25	1100

DP, degree of polymerization

were established. The apparent CSF volume established in the current study is within the range of prior reported CSF volumes in the literature in adult rhesus macaques.[20,24,25] A previous study reported a CSF flow rate of 0.034 mL/min without a reported volume[2] in a similar NHP model in which the CSF ventricular reservoir was implanted in the 4th ventricle only. Notable differences in the 2 studies contributing to the differing CSF rates are the method and type of CSF collection, the type of inulin used, and the inulin assay methods. The previous study[2] administered the same dose of inulin, but because administration and collection of CSF used the same site, ventricular CSF and not lumbar CSF was collected, and a sampling bias might have occurred. The type of inulin used for the prior study was a powdered nonUSP grade inulin as compared with our use of USP-grade inulin in a saline solution. In addition, the prior study analyzed inulin with a spectrophotometric technique using an indole 3–acetic acid reaction; in contrast, inulin in our study was analyzed using a specific functional immunoassay (ELISA). Technologic advances in inulin production and analysis as well as advances in this preclinical NHP model enabling intraventricular administration into the ventricles with unbiased lumbar CSF collection via the lumbar port, located caudal to the administration site, contributed to the dichotomy of results.

The position of the CSF ventricular reservoir, located in either the lateral or 4th ventricle, did not contribute to the dichotomy of results between the 2 studies[2] or in the minor variability of results in this study. Prior pharmacokinetics studies in our laboratory with agents administered by using the NHP CSF ventricular reservoir in either location (lateral or 4th ventricle) have demonstrated no notable difference in lumbar CSF concentrations after intraventricular administration.[14,23] This result is attributed to a special feature of the CSF Ventricular Reservoir which is a flexible silicone dome that can be 'pumped,' promoting the flow of CSF within the ventricles and the complete mixing of an agent after intraventricular administration.[24,31]

The total CSF volume in the CNS is consistently being maintained by CSF formation and absorption. To maintain the CSF volume balance during intraventricular administration and lumbar CSF sampling, the administration volume was removed prior to replacement by inulin administration, but the CSF sampling volume was not mechanically restored, given that it would be replaced by physiologic CSF formation. Various mean total CSF formation rates in rhesus macaques ranging from 28.6 to 44.2 µL/min[6,15,18] have been reported in the literature. By using these reported values, the estimated volume replacement time for the individual CSF sample size of 300 µL used for this study would be 6.8 to 10.5 min. In addition, the tolerability of the inulin administration and CSF sampling indicated that the total CSF volume was adequately maintained avoiding any neurologic symptoms.

Plasma samples were collected to evaluate the flow of inulin from the CSF space into the bloodstream.[5] Inulin was detected in the preadministration plasma but not in the corresponding CSF presample of all 3 macaques involved in the pharmacokinetics studies. In addition, the plasma inulin concentrations increased over the 10-h sampling period. A secondary study was done to determine whether the source of inulin in the pharmacokinetics preplasma was the daily feed and whether the prandial state influenced plasma levels when inulin had not been experimentally administered. Analysis of the NHP diet confirmed the feed as the source of the pharmacokinetics preplasma inulin concentrations. Inulin plasma concentrations from the feed varied little to prandial state but varied moderately between macaques. This variation was expected because the quantity of the feed provided and ingested was not experimentally controlled. However, other possibilities are potential individual variability in absorption and elimination of dietary inulin. However, dietary inulin did not affect the CSF pharmacokinetics evaluation of inulin administered via the intraventricular route, because inulin was not detected in CSF prior to intraventricular administration.

The limitations of this study are that all of the subjects were male, and only a limited number of macaques were used. In addition, NHP in the study received intraventricular inulin administration during ketamine sedation, and they had been used previously in pharmacokinetic studies with chemotherapeutic agents. We chose to use a total of 5 subjects (3 for pharmacokinetics and 2 for dietary studies) because we viewed this number as sufficient to provide a statistical mean, SD, and CV, and therefore we minimized our use of a higher order species that had required complex surgical instrumentation to provide CSF access. In addition, the small subject number was mitigated by the extensive CSF sampling schedule. CV is the ratio of the SD to the mean and indicates the degree of difference within the data. The CSF pharmacokinetics values observed from the sample concentrations (C_{max} and T_{max}) varied slightly more than the calculated CSF pharmacokinetics values (AUC, $t_{1/2}$, clearance, and V_d), which were notably below 20% CV or varied only marginally, indicating that the number of subjects was sufficient for the pharmacokinetic study.

The NHP CSF access models developed in our laboratory use male rhesus macaques only. Although one study has reported that juvenile and young adult male rhesus macaques (age, 1 to 7 y) have a whole brain volume, determined via MRI (1.5-T T1-weighed scans) that are 20% greater than in age-matched females, that report does not mention a corresponding CSF flow rate or apparent volume described in relationship to brain volume.[8] However, we plan to include female macaques in future pharmacokinetics studies.

The literature reports that ketamine, alone and in combination with other anesthetic agents, decreases parenchymal CSF circulation in mice and NHP during anesthesia. This effect is dose-proportional: higher doses of an anesthetic agent further reduce parenchymal CSF circulation.[9] For our current study, although intraventricular administration was performed during ketamine sedation, the plasma and CSF sampling for 0 to 10 h was done with nonanesthetized NHP. Because the effect of ketamine on CSF circulation was noted only during anesthesia, the influence on the determination of the CSF flow rate and apparent volume in our study would be minimum and constrained to the short period after administration and the collection of the 24-h sample at the end of the study.

The NHP CSF access models were developed as preclinical survival models intended for judicious reuse in multiple studies, and these animals had been used in prior pharmacokinetics studies predominately with chemotherapeutic agents. Procedures, such as veterinary physical and neurologic examination, chemistry and CBC analyses, and a sufficient washout period between agents (determined according to the prior agent's $t_{1/2}$), are rigorously used to ensure that each macaque has returned to their physiologic and neurologic baseline prior to use in a subsequent study. We used these criteria to determine which macaques were eligible for the current study. Although we cannot substantiate that prior use of these macaques affected the results of the current study, this NHP model has been highly predictive of human pharmacokinetics studies and potential clinical trial outcomes[3] when used in this manner.

Because IT administration, both intraventricular and intralumbar, of an agent is frequently performed in preclinical studies to evaluate pharmacokinetics and pharmacodynamics, the parameters of CSF flow rate and apparent volume are essential for optimal study design. The CSF flow rate, determined by the clearance of an inert agent such as inulin, establishes a parameter that is not affected by secretion and absorption of CSF and provides information regarding the potential mechanism of clearance for an agent after intrathecal administration. Clearance of an agent that notably deviates from the CSF flow rate indicates another means of elimination from the CSF system (ventricular, lumbar, and subarachnoid), which may be absorption, degradation, or both, in addition to that of CSF flow and production.

The apparent volume, determined by using the V_d of inulin for this study, provides a critical parameter for calculating a therapeutic IT dose aimed at avoiding inadequate and toxic dosages in preclinical models. Knowing the in vitro concentration of an agent necessary for response against a CNS disease together with the apparent total volume of the CSF system enables the calculation of an appropriate IT dose, rather than one based solely on body weight or surface area. IT dose determinations based on a percentage of the total dose per body weight or body surface (in m^2) are subject to error, potentially resulting in the

lack of clinical effect or toxicity, as the CSF total volume is not dependent on body weight or body surface.

In conclusion, the CSF pharmacokinetics of inulin administered intrathecally via the intraventricular route, with lumbar CSF collection established a mean CSF apparent volume of 10.17 mL and mean CSF flow rate of 0.018 mL/min in adult male rhesus macaques. Dietary inulin produced prolonged plasma inulin concentrations that precluded pharmacokinetic analysis and may affect other preclinical studies involving inulin.

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