Possible Treatment of Parkinson's Disease with Intrathecal Medication in the MPTP Model

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INTRODUCTION

Parkinson's disease is a neurological syndrome secondary to diminished levels of dopamine in the corpus striatum of the cerebrum.[1] This disease is manifested by the classic clinical constellation of bradykinesia, rigidity, tremor and postural changes. The treatment of Parkinson's disease was significantly advanced with the introduction of levodopa, a metabolic precursor of dopamine. However, after five years of levodopa therapy, 50% of patients develop fluctuating motor responses, the "on-off" phenomenon, to drug treatment which can be disabling and in many cases poorly controlled by conservative therapy.[2] These fluctuations range from excessive involuntary dyskinetic movements to akinesia. Since plasma levels of levodopa are high during periods of mobility with dyskinesias and low during episodes of immobility, a constant drug infusion may provide stable plasma drug levels and control this clinical problem.[3]

Several investigators have used a constant intravenous infusion of levodopa to control the "on-off" phenomenon in Parkinson's disease patients.[4] Recently continuous subcutaneous infusion of the dopaminergic agonist lisuride has been reported to control fluctuations of motor performance in clinical trials.[5] In an animal model of Parkinson's disease the direct infusion into the corpus striatum of dopamine has been reported to reduce apomorphine induced rotation in rats with unilateral substantia nigra lesions from 6-hydroxydopamine.[6] Initially the intraventricular application of dopamine was attempted in our laboratory to reverse the symptoms of bradykinesia in the 1-methyl-4-phenyl-1,2,5,6 tetrahydropyridine (MPTP) model of Parkinson's disease in the rhesus monkey. MPTP is a byproduct of improper meperidine synthesis and causes a permanent parkinsonism syndrome in intravenous drug abusers.[7] Subsequently this compound has been used extensively in primates to effect the best animal model of Parkinson's disease, both symptomatically and pathologically, developed to date.[8] However, the use of dopamine caused many undesirable behavioral side effects which caused us to look for a better agent. Since levodopa is relatively insoluble, we decided to look at other possible precursors of dopamine. For the past two years our laboratory has concentrated on the intraventricular administration of levodopa methyl ester (LDME) to reverse the symptoms of bradykinesia induced by MPTP. Additionally, we have investigated the regional advantage of the intraventricular route over intravenous administration. This report will detail our preliminary experience with this model and discuss the potential treatment advantages of intraventricular perfusion in the treatment of "on-off" phenomenon of Parkinson's disease patients.

ACUTE INTRAVENTRICULAR INFUSION

Ten adult rhesus monkeys were administered 1.4 mg/kg MPTP (Aldrich Chemical Co., Milwaukee, WI) intravenously in divided dosages which resulted in the development of severe bradykinesia and marked decrease of spontaneous food intake. The absolute amount of MPTP required to develop clinical parkinsonism showed marked individual variation which correlated primarily with the animal's age with younger animals requiring more drug to exhibit the equivalent motor changes of the treated older animals. All animals required supplementary nasogastric tube feedings in the attempt to maintain pretreatment body weight.

The animals subsequently underwent placement of a lateral ventricular cannula connected to a subgaleal Rickham reservoir or an Infusaid Model 400 pump (Infusaid Corp., Norwood, MA) placed subcutaneously in the interscapular space. All surgery was performed using intramuscular ketamine 10 mg/kg and xylazine 2 mg/kg anesthesia. Postoperatively the animals received acetamenophen water for analgesia. The Infusaid pump permitted the continuous perfusion of artificial cerebrospinal fluid between injections of intraventricular levodopa methyl ester which prevented catheter occlusion whereas the Rickham reservoir permitted frequent CSF sampling following drug injection. Following catheter placement the animals underwent air or positive contrast ventriculography under intramuscular ketamine 10 mg/kg anesthesia to document proper catheter placement.

Prior to LDME injection animals were videotaped for three hours to document spontaneous motor activity. Daily voluntary food intake by the animals was recorded. Following the intraventricular injection of LDME 15 mg, animals were videotaped for an additional three hours. Spontaneous motor activity of the animals was evaluated by a neurologist in a blinded manner and circling movements were measured. Changes in spontaneous food intake were evaluated by a review of the animal's daily food intake records.

CSF dopamine metabolite studies were performed following the evaluation of motor and feeding effects of intraventricular LDME. MPTP-treated rhesus monkeys with Rickham reservoirs connected to lateral ventricular catheters were placed in monkey chairs during CSF sampling experiments. Control CSF 1 ml was obtained immediately preceding the intraventricular injection of LDME 15 mg. Following the injection hourly samples of CSF were obtained for the measurement of the dopamine metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) and LDME using a HPLC system with an electrochemical detector.

After the drug trials the animals were euthanized. The brains were immediately removed and placed in formalin 15%. After adequate fixation gross and microscopic examination were performed.

Review of six animals videotaped before and after intraventricular LDME documented a 470% increase in spontaneous circling movements during the three-hour observation period after injection (FIGURE 1). Analysis of the animals' movement did not reveal circling predominantly in one direction. Hourly measurements of movements after injection were compared to corresponding hours prior to the drug and were analyzed statistically using the Student's T Test. The increase in spontaneous movement was statistically significant ($p < 0.05$).

During the three-hour videotaped observation following intraventricular LDME the animals were noted to increase their spontaneous food intake greatly. Analysis of this behavioral change revealed a 580% increase of food intake during the day of the drug trial compared to the day before (FIGURE 2). The measurement of food intake of the day of the drug trial and the days before and after intraventricular LDME were

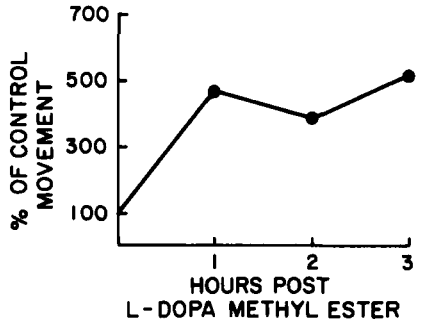

FIGURE 1. Increase of movement following the acute intraventricular injection of LDME measured as percentage of control movements counted in the same MPTP rhesus monkey immediately before drug trial (n = 6).

compared with the Student's T Test and the increase of spontaneous food intake was significant ($p < 0.01$).

CSF dopamine metabolite studies have been completed thus far on two animals. A 10-fold increase in HVA and DOPAC over baseline values after intraventricular LDME have been documented (FIGURE 3). Following intravenous LDME 15 mg minimal increases of CSF HVA and DOPAC were seen and no change of CSF dopamine metabolites were found following an intraventricular placebo injection of artificial CSF (FIGURE 4).

DISCUSSION

Hypotheses of the etiology of the "on-off" phenomenon are based on the factors of drug absorption and transport competition causing fluctuations of levodopa plasma levels as well as alterations of dopamine receptor site function.[9,10] Dietary intake of amino acids can interfere with drug absorption and transport and result in unstable blood levels of levodopa. Plasma levels of levodopa rise more rapidly after oral administration in patients on chronic compared to those patients initiating treatment. Lastly, some authors have proposed that leveodopa therapy results in dopamine receptor site hypersensitivity which would exaggerate the problems of unstable drug plasma levels. Measures used to treat the "on-off" phenomenon have included drug holidays, the administration of frequent, small dosages of levodopa, the use of decarboxylase inhibitors to limit peripheral metabolism, dopaminergic agonist thera-

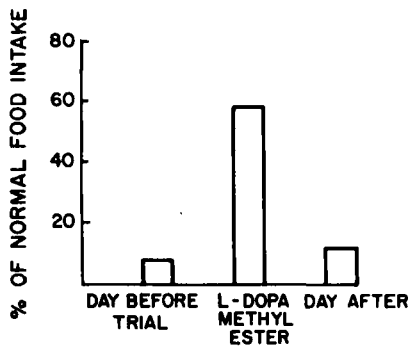

FIGURE 2. Spontaneous food intake measured by volume of the test animals on the days of the drug trial and the days before and after measured in percent of food intake expected of a normal weight matched rhesus monkey (n = 6).

py, and low protein diets.[3] These treatment regimens usually provide only limited control of the symptoms of the "on-off" phenomenon. More recently time-released levodopa has undergone clinical trials and has shown limited success.[11,12] The use of constant drug perfusion would be the obvious extention of these therapies and would avoid the problems associated with oral administration.

Clinically the use of an intravenous infusion of levodopa has been reported by several authors.[4,13] This approach would not be practical for chronic treatment since levodopa is poorly water soluble and acidic and requires large volumes of solution for parenteral administration. More recently a report of constant subcutaneous infusion of the dopaminergic agonist lisuride was published.[5] For a period of 4 to 7 months three patients received lisuride by a portable mini-infusion pump in addition to oral levodopa and a decarboxylase inhibitor. Although symptomatically improved, the patients exhibited increased dyskinetic movements.

In animal models of Parkinson's disease the intraventricular and direct tissue infusion routes have been recently reported.[6,14] Theoretically the intraventricular route of drug administration should be particularly advantageous in the treatment of the

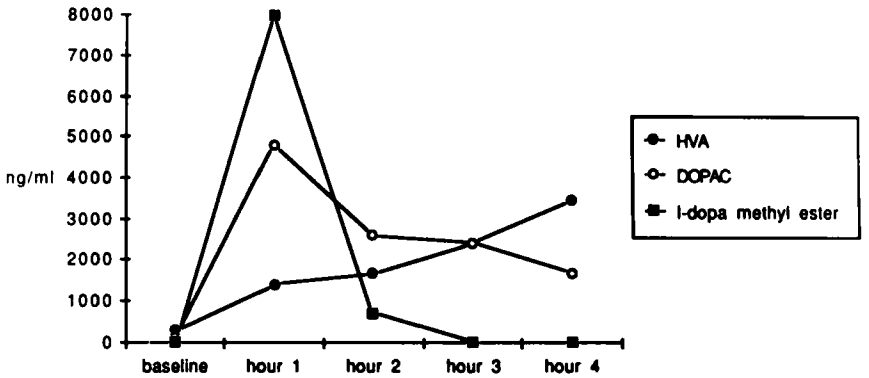

FIGURE 3. Cerebrospinal fluid dopamine metabolites HVA and DOPAC and the test drug LDME in ng/ml measured hourly before and after intraventricular injection of 15 mg.

"on-off" phenomenon. This route would avoid drug absorption and transport competition which in part result in unstable plasma drug levels. Secondly, peripheral metabolism would not be an issue with direct central nervous system administration. These two hypotheses of the "on-off" phenomenon would not be completely avoided using a constant subcutaneous or intravenous drug infusion. The intraventricular route may provide constant drug perfusion for the entire corpus striatum which would not occur with direct tissue infusion unless multiple catheters were utilized. However, a diffusion gradient from the ventricular system may become a significant issue when this route is used in the larger human brain resulting in differential stimulation of dopamine receptors. This concern will require human trials to determine if it will be clinically important.

Direct intrastriatal perfusion of dopamine would require multiple catheters to deliver the neurotransmitter to the widespread parts of the corpus striatum. Placement of these catheters would have to be precise since the tissue diffusion of dopamine was very limited. The necessity of multiple catheters and precise localization would result in a more hazardous procedure with a higher failure rate.

Our preliminary data suggest that the acute intraventricular administration of LDME transiently reverses bradykinesia in the MPTP rhesus monkey model of parkinsonism. An approximate 10 to 1 regional advantage was seen when comparing dopamine metabolites following administration of identical intraventricular or intravenous dosages. This regional advantage is particularly important since implantable pump systems have a limited capacity and the risk of infection occurs with every pump refill. Importantly, LDME is freely water soluble and could be infused in small,

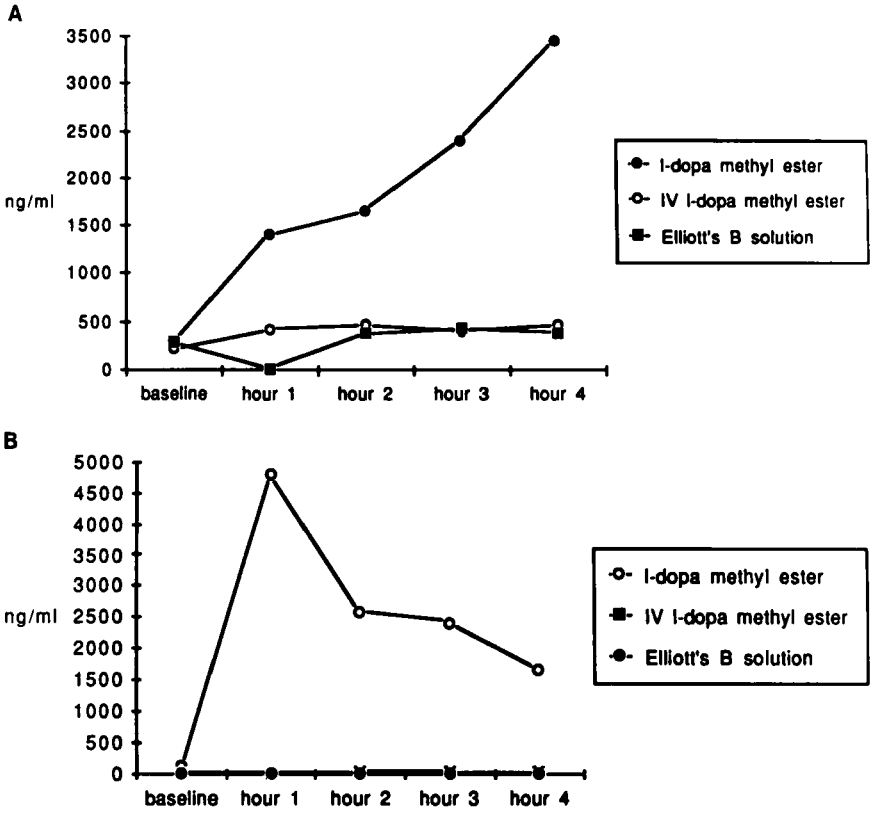

FIGURE 4. Cerebrospinal fluid analysis of (A) HVA and (B) DOPAC in ng/ml measured hourly following intraventricular (I) LDME 15 mg, intravenous (IV) LDME 15 mg and the intraventricular injection of a placebo, Elliott's B solution.

concentrated volumes which is not possible with levodopa. More clinical experience will be necessary to determine if LDME like levodopa is generally better tolerated than many of the dopaminergic agonists.

Additional research is necessary to determine if this therapeutic approach will be practical for patients. The issue of drug stability in solution for periods of three to four weeks will have to be resolved. Additionally chronic efficacy and toxicity will have to be determined before widespread clinical use will be approved. Our positive experience

with the intraventricular administration of LDME warrants its further investigation in the attempt to find a therapy for the problem of "on-off" phenomenon.

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