



Standard Operating Procedures for the use of 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) in nonhuman primates

363.1 Background

Parkinson's disease is a devastating brain disorder. Investigations to generate new treatment options for this disorder have a high research priority. Since its introduction in the early 1980s, the MPTP-treated primate has become a 'gold standard' model for the motor dysfunction in Parkinson's disease (parkinsonism). The most important cellular effect of MPTP in primates is that it lesions dopaminergic neurons, very similar to the pathologic hallmark lesion that is seen in the human disease.

There are three major potential issues with the use of MPTP in primates: (1) It is difficult to induce a stable moderately parkinsonian state with a single (large) systemic injection of this toxin, as animals often recover from the initial state of parkinsonism over the course of several weeks; (2) Individual animals differ greatly in response to the toxin; (3) If treated with high doses, animals can become severely parkinsonian.

The use of multiple smaller injections of the toxin, dosed to the animal's response, provides researchers with more control over the animal's clinical status, addressing all three issues. It is also possible to induce more focal lesions of the dopaminergic system with unilateral intracarotid injections of the toxin, resulting in parkinsonism that affects mostly the side contralateral to the injection. While potentially less clinically invasive this treatment modality requires a vascular surgery, often results in non-parkinsonian features (such as appendicular dystonia), and is commonly associated with near-complete recovery.

These guidelines recognize the scientific value of the MPTP model of parkinsonism, and attempt to address the above-mentioned practical problems associated with the use of this agent.

363.2 Standard Operating Procedures

363.2.1 Prior to MPTP injections, the animal's baseline weight needs to be determined. The baseline weight is the mean of three consecutive weight measurements, taken while the animal has free access to food, during the two-week period preceding the injections. In young animals, growth-related weight increases must be taken into consideration. Thus, in these animals all weight comparisons after the MPTP treatment must be based on weight projections using nomograms.

363.2.2 The dose requirements for successful MPTP treatments differ between primate species, and may also depend on the age of the animal and other factors. The total daily dose, given by systemic injections or other routes, must not exceed 0.8 mg/kg and the total weekly dose should not exceed 2.5 mg/kg in these animals.

363.2.3 The use of high cumulative lifetime doses of MPTP needs to be closely coordinated with the veterinary staff. If plans are made to administer MPTP in excess of a cumulative lifetime dose of 15 mg/kg, the veterinary staff needs to be consulted well in advance. The attending veterinarian will then determine whether the animal is able to tolerate additional MPTP treatments prior to each additional MPTP injection, and/or whether the investigator needs to seek IACUC approval before additional MPTP doses can be administered.

363.2.4 During the acute phase of MPTP effects (i.e., until 72-hours after the last MPTP injection), the care of the animals is supervised by the veterinary staff. Thereafter, the animals are cared for in their normal colony environment. During any of these phases they may need food supplementation or treatment with dopaminergic medications. The need for this is determined through discussions between the veterinary staff and the PI. If supplemental feeding or medication treatments are deemed necessary, it is the PI's responsibility to arrange for these supplemental feedings or medications to be given by either the veterinary staff or qualified research personnel.

363.2.5 All MPTP injections must be documented. At all times, a copy of the documentation must be accessible to the veterinary staff and the research staff. In addition, at Yerkes, this information should be provided to ARMS for timely entry into their system. The documentation must include the following information:

- a. Clinical state of the animals, weight: Records regarding the clinical state of the animal must be updated daily until the state of the animal has stabilized (judged through clinical observations and standardized rating methods) and weekly thereafter. The weight of the animals must be documented at least weekly throughout the acute phase of the MPTP treatment, and quarterly once the animals has developed a clinically stable state.
- b. Food consumption: Food intake charts have to be maintained for at least the first 72 hours after an MPTP treatment. The veterinary staff in consultation with the PI may determine that food intake charts beyond 72 hours are necessary.
- c. Detailed records of medication use: This includes specifics as to the time the medication was given, the type of medication used, the route of administration, and the amount given.

363.2.6 MPTP-treated animals will be treated with dopaminergic medications (either levodopa or dopaminergic agonists) for as long as they are unable to maintain their weight with no more than 20% weight loss compared to the pre-treatment baseline, or show clear clinical signs of distress such as distress vocalization.

363.2.7 If an animal is akinetic for greater than a 60 minute block of time in a 24 hour period, dosage of anti-parkinsonian medication must be adjusted (e.g. by altering administration times, dosages or drugs).

363.2.8 Animals judged to be in pain by the vet staff and/or the research staff will be treated with analgesics in addition to the dopaminergic medications mentioned above.

363.2.9 The following specific endpoints apply to non-human primates treated with MPTP:

- a. Weight loss: Animals must be euthanized if they lose more than 25% of their baseline body weight (as defined under item 1).
- b. Persistent anorexia: Anorexia is defined as the inability of the animal to voluntarily consume enough food to maintain its body weight. Animals requiring mechanically assisted feeding (i.e., tube or gavage feeding) for more than seven continuous days or ten days in a four-week period will be euthanized. If voluntarily accepted by the monkey, syringe feeding can be used for a more extended period of time. Partial supplemental feedings such as high-caloric supplements or the use of primate treats/fruits to maintain the animal's health are also permissible beyond the 7-day period. Similarly, animals can be maintained beyond the 7-day endpoint if they are able to maintain their weight with the help of dopaminergic medications.
- c. Severe parkinsonism: If despite the use of anti-parkinsonian medication, the animal is impaired enough to have extreme difficulty managing normal or everyday situations (e.g. entering or exiting a transfer box or primate chair, interacting with enrichment or personnel, taking medication) for six months (without interruption), the animal needs to be euthanized.
- d. Medical conditions that are repeated and/or unresponsive to clinical treatment.

363.2.10 Scientific justification must be provided to the IACUC if any of these guidelines cannot be adhered to.

363.3 Document Properties

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