SELF ADMINISTRATION IN CYNOMOLGUS MONKEYS (*Macaca fascicularis*)

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**Introduction**

The purpose of this study was to set up and validate a refined model of self administration (SA) in Cynomolgus monkeys.

The goal was to develop an experimental design:
- which allows the animal to free move about avoiding any stressfull condition.
- a study design with a short evaluation duration of any possible drug abuse liability of a new test item.

1. A vascular access port is implanted and connected to an ambulatory pump.
2. A box equipped with a retractable lever avoiding any risk of overdosing and a counting system to record the number of pulls made by the animal. Animal is also observed by a video system.
3. When the animal pushes on the lever of the box, a radio signal is sent to the ambulatory pump and one injection is done.

→ The animal is free to move about avoiding any stressfull condition.

**Animals and surgery**

*Animals:* Male and female Cynomolgus monkeys (*Macaca fascicularis*, old Java monkey) are housed in a controlled environment with temperature (20-24°C) and 12 hours light/dark cycle (light off at 7:30 pm).

*Implantation of the vascular access port:* Implantation is performed under aseptic conditions and recovery are allowed after surgery before starting of the test.

**Study design**

The test design includes 4 phases (Fig 1):
- *Exploration phase:* within the first days, the animal plays with the lever (no injection).
- *Extinction phase:* disinterest of the animal for the system (the number of pulls decreases down to 0) (no injection).
- *Evaluation of vehicle then test item:* 1 At this requirement is achieved, the test item is tested. Each dose level is tested over 2 days in case of absence of effect. In case of an addictive drug, self administration behaviour is observed through an increase in the number of pulls of the lever. The test session is increased up to 5 days with the same dose.
- *Reinforcing power:* evaluated under the same experimental conditions as in the evaluation phase of vehicle and test item but without injection when the animal pushes on the lever.

**Choice of doses**

Each animal will be given increasing doses of the test item [1], according to a close progression, for instance 1/4 log: 0.1, 0.18, 0.3, 0.56 and 1 mg/kg.

**Results: cocaine evaluation**

*Fig 1: Typical profile of the test with an addictive test item*

[Dosing protocol:]
- Each day of the test, the jacket and the pump were put on the animal. Then, the box was put in front of the cage for 2 hours. The system was programmed in order to inject the vehicle or cocaine every 20 minutes avoiding the risk of overdosing with cocaine (i.e. maximum 6 injections by test session).
- The exploration and extinction phases lasted between 5 and 20 days (n=12).
- Cocaine induced a self administration behaviour at 0.56-1 mg/kg/injection (n=3).
- Reinforcing power of cocaine lasted 20 days.

**Discussion**

The main outcome of the test item evaluation phase is the achievement of addictive effects expected with cocaine supporting the validity of the experimental condition applied for assessment of such effects. In addition, these results support that the other goal of this work, design of a device which allows running of the test in a totally free animal, was also achieved.

Regarding the experimental design, the exploration and extinction phases showed that their duration was markedly animal dependent and occasionally individuals are completely disinterested by the system or on the contrary do not stop playing with the lever, suggesting the need for animal selection before inclusion in an experiment. The reinforcing power evaluation is important to well characterise the drug abuse liability of a substance and as expected cocaine had a marked reinforcing power.

**Conclusion**

These results suggest that the method is sensitive enough to detect any possible abuse potential of a test item. The main advantages are the short duration of the evaluation (completed within less than 3 months) and the absence of restraint conditions during the test which increases the quality of the experimental conditions from a humane point of view.

**Reference**