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Assessment of drug dependence potential in rhesus monkeys and rats

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Drug dependence has two aspects as physical and psychological dependence. It is well known that both physical and psychological dependence are developed by central nervous system (CNS) effects, indicating that the target compounds for assessing drug dependence potential are those with CNS effects.

Drug dependence studies in the pre-clinical assessment have not been discussed in the International Congress of Harmonization, resulting in different regulations of the executive authorities in Japan, USA, and Europe. In Japan, Notification No. 113 ("Yakuma" Mar. 14, 1975, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Japan) came in effect as a guide for conducting clinical and pre-clinical studies. The latter part refers to the assessment of acute CNS effects, development of tolerance, and physical and psychological dependence potentials. Pre-clinical studies are conformed to GLP. However, this is not a strict guideline so that researchers can modify investigative methods according to the progress in the methodology and/or accumulation of up-to-date scientific knowledge. In the USA, "Draft Guidelines for Abuse Liability Assessment" was published by Subcommittee on Guidelines for Abuse Liability Assessment, Drug Abuse Advisory Committee, Food and Drug Administration, U.S. Public Health Service in 1990. This guideline describes that the overall profile of

action of a test compound is to be observed first and when there are appropriate indications in the overall characterization it may be necessary to proceed more intensively to collect data on reinforcing, subjective, and discriminative effects. It is neither possible nor desirable at this time to provide a "cookbook" recommendation on specific tests to be performed. Rather, a considerable degree of scientific flexibility with respect to precise methods must be retained, and that these guidelines will focus upon the types of issues to be addressed rather than the specific methods to be used. Ten years later, the committee withdrew the guidelines. In Europe, it appears that there is no guideline for drug dependence potential assessment.

We have been conducting drug dependence studies by our own methods for more than 25 years now in Japan. In our laboratory, the reinforcing effect is investigated by drug self-administration experiments in rhesus monkeys and physical dependence potential by drug-admixed food method in rats.

Drug self-administration experiments in rhesus monkeys

An indwelling catheter is implanted into the jugular or femoral veins of monkeys and when the animals press a lever switch located in their cages, a fixed volume of drug solution is delivered through the catheter (Deneau et al., 1969). Animals: rhesus monkey is the most suitable species for investigating the reinforcing effect of drugs since it is well known that rhesus monkeys actively self-administer almost all dependence-producing drugs that have been abused by humans. Unit dose: the compound possessing the reinforcing effect produces an inverted U-shape dose-response curve since intake rates become low at small unit doses due to a marginal

reinforcing effect and also at large unit doses due to satiation and/or toxic effect. Fig. 1 shows an inverted U-shape dose-response in intravenous self-administration of sodium pentobarbital and pentazocine in rhesus monkeys. Therefore, an appropriate selection of a test dose-range is important to assess the reinforcing effects of newly developed compounds. We demonstrated that the most frequently self-administered dose ranges of cocaine, sodium pentobarbital, pentazocine, nicotine and caffeine were from 1/8 to 1/256 of the threshold doses in gross behavioral observations of each drug, suggesting that a broad dose range, which is less than a quarter of the threshold doses should be used in intravenous self-administration experiments for assessing the reinforcing effect of a drug. Route: intravenous route is the most suitable route for investigating the reinforcing effect, since CNS effects appear immediately after pressing a lever switch. Intragastric route is used for insoluble compounds. Infusion speed: drug self-administration rate is also influenced by infusion speed of compounds. It was reported that the daily number of intravenous self-administration of nicotine at 30 μg/kg/infusion significantly decreased when the infusion speed was changed from 5.2 μg/sec to 1.3 μg/sec, and then at 0.3 μg/sec (Wakasa et al., 1995). The plasma level following a single-dose infusion of nicotine at 30 μg/kg/infusion positively correlated with the infusion speeds. These results indicate that the reinforcing effect on nicotine is a function of the infusion speed, most likely through elevation of the peak level of nicotine in the plasma. Experimental schedule: In USA, the substitution procedures are widely used to assess the reinforcing effect. By this procedure, a test compound at a unit dose is substituted for a baseline drug when self-administration rate of a baseline drug

reaches to a stable and high level. This substitution is frequently repeated with several unit doses of the test compound, wherein the reinforcing effect of a test compound in a wide-range of unit doses can be investigated in a relatively short period. However, there is a possibility that a baseline drug may influence self-administration rate of the test compounds: false positive and/or false negative. In our laboratory, around-the-clock continuous self-administration without any limitation of self-administration dose is also conducted to investigate the reinforcing effects more intensively and to observe gross behavioral changes attained by self-administration of test compounds.

Drug-admixed food method in rats

Physical dependence potential is investigated in CNS-depressing compounds since typical withdrawal signs have been observed in CNS-depressing drugs such as opiates, barbiturates, benzodiazepines, and alcohol. Persistence of CNS-depressing effects is an important factor for the development of physical dependence, indicating that appropriate dosing schedule of a test compound is needed for a physical dependence-producing test. Drug-admixed food method has demonstrated not only evident withdrawal signs of opiates and barbiturates but also weak withdrawal signs of diazepam. Development of physical dependence is assessed through gross behavioral changes, body weight and food intake during withdrawal period. Fig. 2 shows decreases in food intake and body weight during withdrawal period in rats treated with diazepam-admixed food for 4 weeks.

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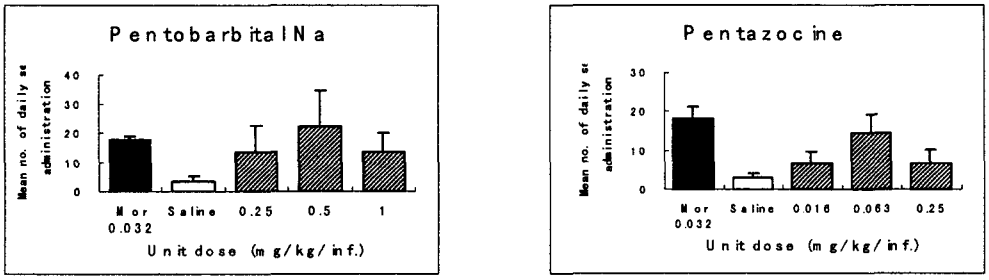

Fig.1 Intravenous self-administration of sodium pentobarbital (left) and pentazocine (right) under a fixed-ratio 5 schedule of reinforcement with 1-min timeout period after each administration during daily 2-h experimental sessions

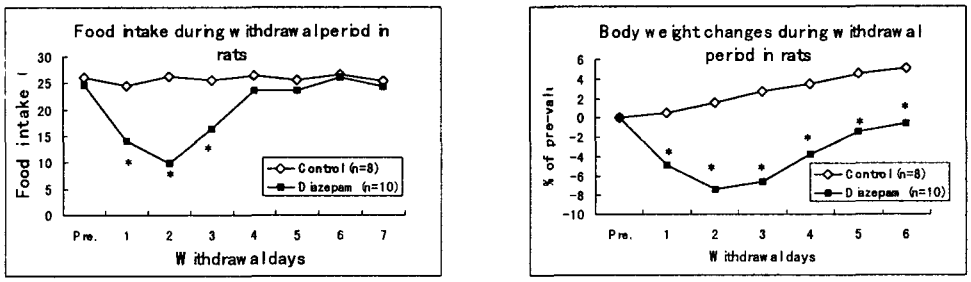

Fig. 2 Changes in food intake (left) and body weight (right) during withdrawal period in rats treated with diazepam-admixed food for 4 weeks.