Short Communication

Effect of a Novel Potential Atypical Antipsychotic Drug, Y-931, in Producing Dystonia in Cebus Monkeys

Yasuyuki Shiigi1,*, Jun-ichi Maeda1, Hiroshi Yasumatsu1, Hiroshi Tanaka1, and Daniel E. Casey2

1Research Laboratory I (CNS), Pharmaceuticals Research Unit, Research & Development Division, Mitsubishi Pharma Corporation, 7-25, Koyata 3-Chome, Iruma, Saitama 358-0026, Japan
2Mental Health Division (P3MIRECC), Veterans Affairs Medical Center, 3710 SW, US Veterans Hospital Road, Portland, OR 97239, USA

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Abstract. The effect of Y-931 (8-fluoro-12-(4-methylpiperazin-1-yl)-6H-[1][benzothieno[2,3-b][1,5]benzodiazepine maleate), a novel potential atypical antipsychotic candidate, in producing dystonia in Cebus monkeys was investigated. Y-931 induced relatively weak dystonia in several observation periods at doses greater than 0.1 mg/kg, i.m. Although Y-931 significantly increased total dystonia scores (the sum of 15 to 360 min after injection) at doses greater than 0.5 mg/kg, i.m., the scores did not exceed 20, up to a dose of 1.0 mg/kg, i.m. and lacked a dose-response relationship. The present result suggests that Y-931 is predicted to have a low risk of extra-pyramidal side effects.

Keywords: Y-931, dystonia, monkey

Although typical antipsychotic drugs have been the primary form of pharmacotherapy for psychosis, they have many undesirable side effects represented by the extrapyramidal symptoms (EPS). EPS are one of the major reasons why patients discontinue their antipsychotic drugs. Investigations of EPS in nonhuman primates have many advantages. Namely, identical symptoms, such as dystonia and parkinsonism, occur in patients and monkeys over similar time courses. Additionally, there is a close correlation between drug type, dose, and the liability of producing EPS (1 – 4).

Y-931, 8-fluoro-12-(4-methylpiperazin-1-yl)-6H-[1]benzothieno[2,3-b][1,5]benzodiazepine maleate, is a novel potential atypical antipsychotic drug candidate interacting with multiple neurotransmitter receptors such as dopaminergic, serotonergic, α-adrenergic, muscarinic, and histaminergic receptors, which is similar to that of clozapine, an atypical antipsychotic drug (5). Y-931 is active in conventional tests indicative of potential antipsychotic activity such as inhibition of apomorphine-induced hyperactivity and suppression of conditioned avoidance response. In models of N-methyl-D-aspartate (NMDA) receptor hypofunction, Y-931 demonstrated a potent protective action against the dizocilpine-induced neurotoxicity (neuronal vacuolization) in the rat retrosplenial cortex and reversed the dizocilpine-induced social deficits in rats at the same doses at which their neuroprotective action was exhibited. Since Y-931 does not cause catalepsy in rats despite its potent blockade of D2 receptors, it is predicted that Y-931 shares the benefit of a low risk of EPS with clozapine (5). Therefore, it is of considerable interest to investigate the capacity of Y-931 to cause acute dystonia in nonhuman primates. In the present study, we studied the effect of Y-931 in producing dystonia in Cebus monkeys.

Seven female Cebus albilfons monkeys (Oregon Regional Primate Research Center, Beaverton, OR, USA), 10 – 28-year-old, were used. They were individually housed and tested in their home cages. They were allowed access to food and water ad libitum and were kept in environmentally controlled conditions (06:30 a.m. – 19:00 p.m. lights on, 20 – 23.9°C). They were previously sensitized to haloperidol and known to have stable responses to antipsychotics. The present studies were conducted in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the US National Institutes of Health.
Y-931 (synthesized at Mitsubishi Pharma Corporation, Saitama) was dissolved in 0.1 mol/L citric acid/polyethylene glycol 400 (1:1) solution and injected intramuscularly in a volume of 0.1 mL/kg. The dosages are expressed as being the base equivalent. Dystonia was scored by an experienced rater who was blind to the drug dosage. The observations of dystonia were scored before and 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, and 360 min, as well as 24 h after intramuscular injection of Y-931. Rating of dystonia was recorded using a scale of 0 – 3 (0 = absence of dystonia, 1 = dystonia occasionally present, 2 = dystonia regularly present but interrupted, 3 = dystonia continuously present). Dystonia scores were summed in four body regions (mouth, head and neck, trunk, limbs) in each observation period. Dystonia scores were measured after different doses of Y-931 within the same group of monkeys, with drug dosages repeatedly administered at intervals of more than 6 days in a random sequence. Data were presented as the mean ± S.E.M. at each observation time and the mean total scores ± S.E.M. summed from 15 – 360 min periods. Data were analyzed by a Friedman’s rank test followed by a non-parametric Dunnett’s multiple comparison test. A P value of less than 0.05 (two-tailed) was considered to indicate statistical significance.

Y-931 did not produce notable dystonia up to 0.05 mg/kg, i.m. Y-931 significantly increased dystonia scores in several observation periods at doses more than 0.1 mg/kg, i.m. (Fig. 1A). Y-931 significantly increased total dystonia scores (the sum of 15 to 360 min after injection) at doses more than 0.5 mg/kg, i.m. However, the dose-response curve was flat (Fig. 1B).

Y-931 produced relatively weak dystonia at doses greater than 0.1 mg/kg, i.m. The minimum effective dose for inducing dystonia in Cebus monkeys with haloperidol, a prototype of typical antipsychotic, was 0.025 mg/kg, i.m. (6). Thus, there is approximately fourfold higher threshold dose required for Y-931 to cause dystonia, compared to haloperidol, even though

![Fig. 1. Effect of Y-931 on dystonia in Cebus monkeys. A) Time course, B) Total dystonia score (15 – 360 min). Data are expressed as the mean ± S.E.M. from 7 monkeys *P < 0.05, **P < 0.01, significantly different from the vehicle-treated group (non-parametric Dunnett’s multiple comparison test).](image-url)
the dopamine D2-receptor binding affinity for the two drugs is similar (5). Furthermore, the total dystonia score of Y-931 did not exceed 20, up to a dose of 1.0 mg/kg, i.m., whereas the total dystonia score of haloperidol (0.025 mg/kg, i.m.) was approximately 65 (6). Additionally, the dystonia response of Y-931 lacked a dose-response relationship. A flat dose-response curve is not seen with any of the currently available typical antipsychotics. The flat dose-response curve was due, at least in part, to the decrease in dystonia during the middle part of the test period, followed by a return of dystonia 4–6 h after administration, particularly at doses of 0.25 and 0.5 mg/kg. Although the precise mechanisms are currently unclear, some metabolite(s) of Y-931 may contribute to the return of dystonia. The dystonia caused by the metabolite(s) may predominate later in the test period. Further pharmacokinetic studies are necessary to clarify this issue.

One possible explanation of the unique profile of Y-931 in induction of dystonia is that Y-931 interacts with the receptors, which were hypothesized to be responsible for the low risk of EPS with clozapine, such as muscarinic and serotonin 5-HT2 receptors. It is well known that anticholinergic agents reverse acute dystonic symptoms in patients receiving antipsychotic drugs (7). Similarly, anticholinergic agents reduced acute dystonia induced by antipsychotic drugs in nonhuman primates (8, 9). Thus, the affinity for muscarinic receptor may contribute to the low dystonic potentials of Y-931. Although the hypothesis that 5-HT2 antagonism ameliorates EPS induced by the blockade of D2 receptor has been proposed (10, 11), several authors indicated that this hypothesis was not supported by studies in nonhuman primates (3, 4, 12). Therefore, the affinity of Y-931 for the 5-HT2 receptor may not explain the present result in Cebus monkeys. Another possible explanation is the limbic selectivity of Y-931. An electrophysiological study has shown that chronic administration of Y-931 decreases the number of spontaneously active dopamine cells in the ventral tegmental area (A10) without affecting cells in the substantia nigra (A9) (Minabe and Ashby, submitted), suggesting its analogous limbic selectivity to clozapine (13).

Although the present results indicate that the production of dystonia in monkeys treated with Y-931 is apparently weak compared to typical antipsychotic drugs, such as haloperidol, further investigations are needed to confirm the clinical benefits of Y-931. It is important to determine the separation between benefit (antipsychotic efficacy) and risk (EPS) for Y-931. Therefore, in order to know the effective dose of Y-931 for the antipsychotic action in Cebus monkeys, we need to conduct the tests used to predict antipsychotic efficacy in Cebus monkeys, such as antagonism against amphetamine and/or apomorphine-induced behaviors (14). Furthermore, since the chemical structure of Y-931 is similar to that of olanzapine, which is widely used as one of the atypical antipsychotic agents, the effect of olanzapine should be evaluated using the same monkeys to compare with that of Y-931 in future studies.

In conclusion, although further studies will be necessary to clarify the mechanisms, Y-931 produced only weak dystonia compared to typical antipsychotic drugs and the effects lacked a dose-response relationship. Therefore, the present result further confirmed that Y-931 is expected to have a low risk of EPS in clinical use.

References