Abstract  
Rationale: Previous work has shown that clozapine suppressed tacrine-induced jaw movements at lower doses than those required for suppression of lever pressing. Objective: The novel atypical antipsychotic olanzapine was assessed in these behavioral tests. Methods: The effect of acute olanzapine on the suppression of tacrine-induced tremulous jaw movements was examined. In order to determine the relative potency of this effect compared with other behavioral effects of olanzapine, suppression of lever pressing also was studied. In a second series of experiments, rats received olanzapine for 14 consecutive days to study the effects of repeated injections of this drug on jaw movements and lever pressing. Results: Acute olanzapine administration decreased tacrine-induced jaw movements (ED50: 0.4 mg/kg), and also reduced lever pressing (ED50: 1.12 mg/kg). The ratio of the ED50 for suppression of jaw movements to that for suppression of lever pressing was used as an index of liability to produce extrapyramidal side effects, and the present results demonstrate that olanzapine has a ratio similar to that previously shown for clozapine. In the repeated administration studies, rats were observed on day 13 of drug treatment for the ability of olanzapine to induce jaw movements, and olanzapine failed to induce jaw movements. On day 14, olanzapine reduced tacrine-induced tremulous jaw movements (ED50: 1.12 mg/kg). In a separate experiment, olanzapine significantly suppressed lever pressing, and this effect showed sensitization with repeated administration (day 14, ED50: 0.76 mg/kg). Thus, repeated injections of olanzapine reduced tacrine-induced jaw movements in a dose range similar to or slightly higher than that which suppressed lever pressing. Conclusions: On tests of jaw-movement activity and lever pressing after both acute and repeated drug administration, olanzapine demonstrated a profile somewhat similar to clozapine, and both of these drugs differ substantially from the typical antipsychotic haloperidol.

Key words Schizophrenia · Extrapyramidal · Tacrine · Cognex · Motor · Clozapine

Introduction

Clozapine is an atypical antipsychotic drug, which offers several therapeutic advantages over conventional agents (Kane et al. 1988; Baldessarini and Frankenburg 1991; Miller et al. 1994). Clozapine has a lower liability than typical antipsychotics, such as haloperidol, for producing motor side effects such as parkinsonism or tardive dyskinesia (Marsden et al. 1975; McEvoy 1983; Tarsy 1983; Meltzer 1989; Safferman et al. 1991). In addition, recent evidence indicates that clozapine is effective at ameliorating tremor and other motor dysfunctions in patients with idiopathic Parkinson’s disease (Pakkenberg and Pakkenberg 1986; Bernardi and Del Zompo 1990; Fisher et al. 1990; Friedman and Lannon 1990; Arevalo and Gershani 1993; see review by Factor and Friedman 1997). Considerable research efforts have been aimed at developing new compounds that retain the beneficial aspects of clozapine, but do not induce agranulocytosis (Alvir et al. 1993).

At present, several putative atypical antipsychotic compounds have been synthesized, and one of the most promising is olanzapine (Zyprexa). Olanzapine is a thienobenzodiazepine compound, which has a receptor-binding profile similar to that of clozapine. Olanzapine shows a high affinity for 5-hydroxytryptamine (HT)2A, 2C, and histamine (H1) receptors, and a moderate affinity for dopamine (DA) D2 and acetylcholine muscarinic receptors (Bymaster et al. 1996, 1997; Pilowski et al. 1996; Schotte et al. 1996). Olanzapine also binds to 5-HT6 and α1-adrenergic receptors (Bymaster et al. 1997). Double-blind, clinical studies using olanzapine have shown that olanzapine is highly efficacious as a treatment for psychotic symptoms (Beasley et al. 1996, 1997).
It has been suggested that the ratio of the ED50 for suppression of lever pressing (Trevitt et al. 1997). In previous studies (Trevitt et al. 1997; Nawab 1997; Salamone et al. 1998), the rank order of these ratios was as follows: clozapine < risperidone < thioridazine < fluphenazine < haloperidol. Thus, in the first two experiments, the effects of olanzapine on tacrine-induced jaw movements and lever pressing were studied to determine whether olanzapine shows a clozapine-like profile. In a second series of experiments, olanzapine was administered to rats for 14 consecutive days. Rats were observed on day 13 of drug administration for the ability of olanzapine to induce jaw movements. On day 14, rats were challenged with tacrine to induce a high level of jaw-movement activity in order to study the effect of olanzapine on tacrine-induced jaw movements. Additional groups of rats were used to study the effects of olanzapine on lever pressing. Previous work using these procedures has shown that clozapine failed to induce jaw movements on day 13 and, also, that clozapine suppressed tacrine-induced jaw movements on day 14 (Trevitt et al. 1998).

### Materials and methods

#### Subjects

A total of 84 male Sprague Dawley rats (Harlan Sprague Dawley, Indianapolis, Ind.) with no prior drug experience were used in these experiments. The animals weighed 315–450 g during the course of the experiment and had ad libitum access to lab chow and water. Animals were group housed in a colony that was maintained at approximately 23°C and subjected to a 12-h light/12-h dark cycle (lights on at 0700 hours). These studies were conducted according to University of Connecticut and National Institutes of Health guidelines for animal care and use.

#### Drugs

Tacrine was obtained from Sigma Chemical Co. (St. Louis, Mo.), and olanzapine was generously donated by Lilly Pharmaceuticals (Indianapolis, Ind.). Olanzapine was dissolved in 0.3% tartaric acid, which also served as the vehicle control. Tacrine was dissolved in 0.9% saline. The drug dosages were selected based on previous published reports and pilot work (Salamone et al. 1996; Trevitt et al. 1997).

#### Experimental procedures

### Tremulous jaw movements

Observations of animals were made while they were in a 30x30x30-cm clear Plexiglas chamber with a wire mesh floor, which was elevated 42 cm from the bottom of the table top. This allowed for viewing of the animal from several angles. Tremulous jaw movements were defined as rapid vertical deflections of the lower jaw that resembled chewing but were not directed at any particular stimulus. Each individual deflection of the jaw was recorded using a mechanical hand counter. The observer was blind to the experimental condition of the animal being observed. Separate studies with two observers demonstrated an inter-rater reliability of r=0.92 (P<0.05) using these methods.