Prevention of antipsychotic-induced weight-gain by the 5-HT₆ agonist, E-6837

D.J. Heal¹, S.C. Cheetham², A. Fisas², X. Codony², H. Buschmann²

¹RenaSci Consultancy Ltd, Nottingham, NG1 1GF, UK; ²Laboratorios Dr Esteve S.A., Av Marie de Deu de Monserrat 221, 08041 Barcelona, Spain.

INTRODUCTION

The 2nd generation antipsychotic drugs have provided a significant improvement in schizophrenia treatment by delivering efficacy with a reduced liability for extrapyramidal side-effects (EPS). However, there is a growing awareness that these drugs increase cardio-metabolic risk by causing obesity, dyslipidaemia and Type 2 diabetes.

5-HT₆ ligands, including agonists and antagonists, have been shown to produce hypophagia and substantial weight-loss in rodent models of obesity¹. Depending on the experimental conditions, E-6837 has been characterised as either a partial or full agonist of rat 5-HT₆ receptors, and as a full agonist of human 5-HT₆ receptors².

When given to obese cafeteria-fed rats, E-6837 causes profound hypophagia and weight-loss. In this study, we have explored whether E-6837 will attenuate the hypophagia and weight-gain caused by one of the worst offending 2nd generation antipsychotics, i.e. olanzapine.

**REFERENCES**


MATERIALS AND METHODS

Groups of 10 female, Sprague-Dawley rats (250-300g) were individually housed and maintained on reversed-phase lighting with free access to high-fat chow and water. After 2 weeks acclimatisation, the rats were orally treated at 0h and 6hr for 14 days as follows: vehicle (twice daily); olanzapine (3 mg/kg, morning) + vehicle (afternoon); E-6837 (30 mg/kg, twice daily) or olanzapine (3 mg/kg, morning) + E-6837 (30 mg/kg, twice daily). Rats, feeding jars and water bottles were weighed (to the nearest 0.1 g) every day at 0 h with the final readings on Day 15.

RESULTS

- Compared with the vehicle controls, olanzapine treatment produced a significant 13.3% (p<0.05) increase in average daily food intake in Week 1, but no significant increase in Week 2 (Fig. 2), together with a progressive increase in bodyweight (5.6%, p=0.01 at Day 15) (Fig. 1).
- In contrast, E-6837 when given alone reduced cumulative food intake by 28.3% (p<0.01) compared with the vehicle controls in Week 1 (Fig. 3) and decreased bodyweight by 7.2% (p<0.01) at Day 15 (Fig. 1). Rats treated with the combination of E-6837 + olanzapine experienced reductions of both food intake (19.2%; p<0.01) and bodyweight (6.6%; p<0.02) that were similar to those observed in the rats treated with E-6837 alone (Figs. 1 and 3; Table 1).
- Compared with the rats treated with olanzapine alone, cumulative food intake over Week 1 in the group given E-6837 + olanzapine was reduced by a substantial 28.6% (p=0.001) (Fig. 3) and bodyweight at Day 15 by 11.6% (p=0.001) (Fig. 1).

**SUMMARY**

- E-6837 not only prevented antipsychotic-induced hyperphagia and weight-gain, but it also produced weight-loss that was indistinguishable from the effect observed when the compound was given as monotherapy.
- Based on the currently available data, it is unclear whether the observed effects are mediated by a 5-HT₆ related effect or via other pharmacological mechanisms.
- These data suggest that 5-HT₆ ligands may have the potential to be a viable approach for the treatment of obesity and its metabolic complications in patients treated with 2nd generation antipsychotic drugs.

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