EFFECT OF CHRONIC ADMINISTRATION OF TOPIRAMATE AND PHENTERMINE, ALONE AND IN COMBINATION, IN AN ANIMAL MODEL OF DIETARY-INDUCED OBESITY

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INTRODUCTION

A recent phase 2 clinical study has shown that QnexaTM, a novel proprietary treatment containing topiramate and phentermine, produced significantly greater weight-loss in obese patients than placebo or either drug given alone1. The aim of this study was to evaluate the effects of chronic administration of low doses of the two drugs given both alone and in combination, on body weight and food and water intake in dietary-induced obese (DIO) rats2. This model was employed as the relative abilities of reference drugs to reduce body weight in these animals has been shown to correlate well with their reported efficacy in the clinic3. Female rats are used in the model because they have flatter growth curves than males and it is easier to induce obesity in them. Furthermore, the prevalence of obesity is generally higher in women than in men4.

METHODS

Female Wistar rats (Charles River, 250-300g) were maintained on reverse-phase lighting (lights out 09.30-17.30 h) with free access to powdered high-fat chow, chocolate, peanuts and tap water during the induction of obesity (14 weeks) and throughout the feeding study. After a 7 day run-in period, during which rats were dosed orally with vehicle once daily, rats were dosed orally with vehicle, topiramate, phentermine or topiramate plus phentermine once daily for 41 days. Topiramate was given in a dose of 30 mg/kg (increased to 60 mg/kg on Day 15). Phentermine was given in a dose of 5 mg/kg. Rats, feeding jars and water bottles were weighed every day at the time of dosing which was at the onset of the dark period. Topiramate and phentermine were dissolved in 1% Tylose MH500, 1% polysorbyt (in deionised water; dose volume 1 ml/kg). All doses are for the free base. Data was analysed by one-way analysis of covariance using baseline data as the covariate (ie Day 1 body weights or average food or water intake during Days 6-10). Results are therefore expressed as means (adjusted for differences between the groups at baseline) and SEM (calculated from the residuals of the model). Multiple comparisons were by Dunnett’s test to compare each drug-treatment group with the vehicle-treated controls. Comparisons between topiramate plus phentermine versus either topiramate or phentermine alone were by Sidak’s tests. Separate Sidak’s tests were used to examine whether the effects of topiramate and phentermine were additive or synergistic (ie whether the effects of topiramate plus phentermine were greater than expected from the effect of topiramate alone added to the effect of phentermine alone (when ‘effect’ refers to difference from the control group)).

RESULTS

Fig. 1  Effect of topiramate and phentermine, alone and in combination, on body weight in DIO rats

Fig. 2  Effect of topiramate and phentermine, alone and in combination, on daily food intake in DIO rats

Fig. 3  Food intake data expressed as average daily food intake per week

Fig. 5  Water intake data expressed as average daily water intake per week

**SUMMARY AND CONCLUSIONS**

- Topiramate, phentermine and topiramate plus phentermine significantly reduced body weight (by 6.3%, 7.2% and 15.6%, respectively, vs controls on Day 42). The marked reduction in body weight produced by topiramate plus phentermine was significantly greater than the weight-loss produced by either drug alone.

- Food intake was significantly decreased by topiramate on Day 1 and by phentermine on Days 1 and 8. Neither drug significantly altered food intake in DIO rats (Weeks 5 and 6).

- All drug treatments significantly increased daily water intake. This was particularly evident in animals given topiramate. The increase in water intake produced by the combination of topiramate and phentermine was significantly higher than the increase in water intake in the phentermine group but not the topiramate group (Weeks 5 and 6).

- The effects of topiramate and phentermine on body weight and food and water intake in the DIO rats were additive. There was no evidence of synergy (nearly all of the tests for interactions between the two drugs were not significant).

- These results support preliminary clinical findings that the combination of topiramate and phentermine may be a novel approach for the management of obesity, with similar or even superior efficacy to other drug treatments (10% or more weight-loss in over 50% of patients at 24 weeks7), and demonstrate how animal models can be used to evaluate the weight-loss potential of combination drug therapy.

REFERENCES