Br. J. clin. Pharmac. (1990), **30**, 613–615

Tremor and the anti-obesity drug BRL 26830A

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The thermogenic β_3-adrenoceptor agonist BRL 26830A has been shown to increase weight loss in dieting subjects but tremor was a frequent adverse effect. We have investigated the magnitude and nature of this tremor after a single oral dose in 18 subjects. Two complementary techniques were used to attach the recording apparatus to the subjects to give both isotonic and isometric measures of tremor. Increases of 84% and 40% respectively were found due to exaggeration of physiological tremor presumably mediated through concomitant β_2-adrenoceptor stimulation. The use of β_3-adrenoceptor agonist drugs in the treatment of obesity may increase but the development of an agent without tremor inducing properties would be an obvious advantage.

Keywords tremor adrenoceptor obesity thermogenesis BRL 26830A

Introduction

BRL 26830A, (R*, R*)-(±)-methyl 4-[2-[(2-hydroxy-2-phenylethyl)amino]propyl]-benzoate, (E)-2-butenedioate (2:1) salt, is an adrenoceptor agonist drug whose biological effects are mediated by its free acid metabolite. It is a more potent thermogenic agent than selective β_1- or selective β_2-adrenoceptor agonists but has much less β_1- or β_2-activity. In rodents thermogenesis occurs in brown adipose tissue and BRL 26830A stimulates lipolysis 21-fold more potently than it stimulates atrial rate, a β_1-effect and 8-fold more potently than it induces tracheal relaxation, a β_2-effect (Arch *et al.*, 1984). It was also shown that BRL 26830A is 150 times more selective for lipolysis than isoprenaline. This suggests that the drug is not acting at β_1- or β_2-receptors but at the distinct β_3-receptor which has recently been cloned (Emorine *et al.*, 1989). In man BRL 26830A is also a thermogenic agent which has been shown to promote weight loss in dieting obese subjects and to have little effect on pulse and blood pressure (Connacher *et al.*, 1988). However, in this study and in others (Chapman *et al.*, 1988) the only regularly reported adverse effect was shaky hands and tremulousness suggesting some activity of the drug at skeletal muscle β_2-adrenoceptors. In view of the potential importance of this drug as an anti-obesity agent we have studied the nature and magnitude of tremor induced by a single oral dose of BRL 26830A.

Methods

Eighteen healthy subjects were recruited for the study. Informed consent was obtained from each and ethical approval for administration of BRL 26830A had been given by Tayside Health Board Ethics Subcommittee. Tremor was measured on two occasions and then 50 mg BRL 26830A was given orally. Thereafter measurements were made at 30 min intervals up to 120 min. Tremor was quantified by an apparatus which amplified the frequency band of interest (7–12 Hz) and rejected frequencies outwith this range. The resulting signal was rectified and integrated over a fixed time epoch of 5 s thus providing an

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objective measure of the amount of tremor. Two techniques were used to couple the apparatus to the subject. In one the limb was unrestrained and movement was recorded (isotonic), and in the other the limb was not allowed to move and fluctuations of force were recorded (isometric). Isotonic measurements were made by an accelerometer attached to the outstretched middle finger of the right hand which the subject maintained in an approximately horizontal attitude. Isometric measurements were made by a strain gauge against which the subject pressed with the tip of the same finger to exert a small force of 2 Newtons into extension. The subject was able to regulate this effort by visual feedback from a meter.

Results are expressed as mean (s.e. mean) and statistical analysis was by the Wilcoxon signed rank test. Confidence intervals for mean percent increase in tremor were calculated using the logarithms of the values.

Results

In all but two cases an increase in tremor was detected and in some the increase was by a factor of more than four. The effect usually appeared within 30 min of BRL 26830A administration and was maximal after 90 to 120 min. When assessed isotonically the basal tremor was 31.7 (7.5) cm s^{-2} and the mean increase at 120 min was 84 (20)% (95% confidence interval +45 to +131, $P < 0.01$). Similarly, when assessed isometrically, the basal tremor was 42.1 (3.9) mN and the mean increase at 120 min was 40 (12)% (95% confidence interval +11 to +84, $P < 0.05$). The relative increases in tremor over time are shown in Figure 1. An acceleration spectograph of hand tremor in three subjects showed a clear frequency peak at 8–10 Hz.

There was considerable variation in the basal level of tremor between subjects but there was no correlation between the basal level and the subsequent increase in response to BRL 26830A.

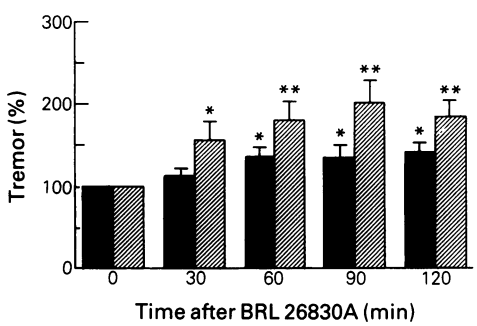

Figure 1 Tremor assessed isometrically (■) and isotonically (▨) expressed as percentage of basal value, mean with s.e. mean bars.
$^{*}P < 0.05$, $^{**}P < 0.01$

Discussion

This study clearly demonstrates that BRL 26830A induces tremor. The frequency of the tremor suggests that it is an exaggeration of physiological tremor and indeed other β-adrenoceptor agonist drugs induce a similar response (Marsden *et al.*, 1967) presumably through a common mechanism which may be β_2-adrenoceptor stimulation. The increased tremor is most evident when assessed isotonically and is less dramatic when the limb is restrained and fluctuating force measured. The reason for this is unclear but the tremor may be driven by feedback oscillations in the stretch reflex, in which case there will be less oscillation if the limb is 'stalled'. An alternative explanation is that there are normally bonds present in relaxed muscle which provide stability and that this thixotropic stabilisation is reduced by these adrenaline-like drugs (Lakie *et al.*, 1984).

During 18 weeks treatment with BRL 26830A tremor was experienced by 12 of the 16 subjects completing the active limb of the study and rated as slight by nine, moderate by two and severe by one (Connacher *et al.*, 1988). Although the tremor decreased with time it was a frequent and clinically significant adverse effect. The magnitude of tremor was similar in this single dose study. Most subjects were aware of a feeling of tremulousness, and characteristically it was of sudden onset, suggesting that a threshold plasma concentration is required to induce the tremor. This effect could perhaps be minimised by starting therapy with a smaller dose or by altering the formulation of the tablet. Alternatively, a drug with more selectivity for the thermogenic β_3-adrenoceptor and less β_2 tremor-inducing effects might be most efficacious. A β_3-adrenoceptor agonist with much less activity on a cat model of tremor has been reported (Holloway *et al.*, 1988) but no human data are available at present.

Past experience with amphetamine abuse and the appreciable side effects of anorectic agents currently in use, such as diethylpropion and fenfluramine, make obesity treatment with thermogenic drugs of considerable interest. However, a preparation without tremor-inducing properties would be an obvious advantage.

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(Received 19 March 1990, accepted 30 May 1990)