The effect of theophylline on thyrotoxic tremor

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- 1 The effects of intravenous aminophylline on theophylline-induced tremor were studied in six hyperthyroid patients before and after treatment to euthyroidism.
- 2 Baseline tremor power was significantly greater in the hyperthyroid compared with the euthyroid state ($P < 0.05$).
- 3 Aminophylline produced a significantly greater increase in tremor power in the hyperthyroid compared with euthyroid state.
- 4 There was a significant increase in plasma theophylline clearance and reduction in $t_{1/2}$ elimination when patients were hyperthyroid but volume of distribution did not change.
- 5 Intravenous aminophylline potentiates the tremor produced in hyperthyroidism despite an increase in plasma theophylline clearance. A pharmacodynamic mechanism is therefore likely.

Keywords hyperthyroidism tremor theophylline

Introduction

The tremor which occurs in patients with hyperthyroidism can now be accurately quantitated and has a similar frequency to physiological tremor but with a considerably greater tremor power (Graham, 1945; Lippold *et al.*, 1959; Marsden *et al.*, 1968; Abila *et al.*, 1985) which is ameliorated by β -adrenoceptor blocking agents (McDevitt & Nelson, 1978). The mechanisms of production of thyrotoxic tremor is not clear. Aminophylline also produces tremor of a similar frequency to thyrotoxic tremor (Abila *et al.*, 1985). Hyperthyroidism increases theophylline metabolism (Bauman *et al.*, 1984). The metabolism of theophylline in both the hyperthyroid (Vozeh *et al.*, 1984) and euthyroid state appears to be related to the free thyroxine concentration (Williams *et al.*, 1987). The present study has investigated the tremorogenic potential of aminophylline on the same group of patients when hyperthyroid and treated to euthyroidism in an attempt to investigate the relationship between the drug and disease induced tremors and throw light on their respective mechanisms.

Methods

Six thyrotoxic patients (five females) aged from 46 to 67 years (median 61 years) and weighing between 52.7 and 75 kg (median 60 kg) were studied. None had any contraindications to theophylline treatment.

Patients were on no other medication when first studied and gave fully informed written consent before taking part. Ethical approval for the study was obtained from the local ethics committee.

Hyperthyroidism was diagnosed clinically and confirmed by an elevation of free triiodothyronine ($FT_3 > 9 \text{ pmol l}^{-1}$) and/or free thyroxine ($FT_4 > 26 \text{ pmol l}^{-1}$). Subsequent treatment consisted of administration of carbimazole and I^{131} where appropriate. All patients abstained from caffeine-containing beverages for 24 h and from carbimazole for at least 3 days prior to the study period. A light breakfast was provided at least 3 h before the study. On two separate occasions, once when hyperthyroid and again when euthyroid, patients were infused with either aminophylline (350 mg

over 15 min via an indwelling cannula placed in the brachial vein of the left forearm) or placebo. Finger tremor was measured with patients in the sitting position, 15 min prior to infusion and subsequently at 15 min intervals up to 90 min using a computer-based accelerometric technique based upon a piezoresistive accelerometer (Type BLA 2, Pye Dynamics Limited) statically calibrated by turning it through 180° and measuring the output producing a 2 g change, and taped to the dorsum of the middle finger of the right hand. The forearm was supported to the wrist by polystyrene foam moulded into the shape of the arm and fixed to the right arm of the chair. The hand was raised from the wrist and held horizontally for 20 s. The signal from the accelerometer was collected during the last 10 s of this period. The hand was allowed to rest for 40 s and the procedure repeated. Five 10 s recordings were made at each assessment point. Peak frequency of tremor and total tremor power from 2 to 14 Hz were determined following spectral analysis of the data using a Fourier transformation of the autocovariance function as previously described (Abila *et al.*, 1985). Since tremor power was not normally distributed, values are described as median and range.

Blood for plasma theophylline concentration measurement was obtained from the cannula at times corresponding to tremor assessment and additionally at hourly intervals for a period of 7 h. Plasma was stored at -20°C until assayed by h.p.l.c. (Grgurinovich, 1986). Pharmacokinetic analysis was performed by least squares linear regression analysis, after correction for the difference in molecular weights of aminophylline and theophylline.

Statistical analysis was performed using the Wilcoxon paired Rank test or Student's paired *t*-test where appropriate.

Results

The peak frequency of tremor in individuals ranged from 6.78–9.86 Hz (median 8.62) when the patients were thyrotoxic and from 6.52–8.2 (median 7.68) when euthyroid. There was no significant difference between the peak tremor frequency before treatment (median 7.31 Hz) and when the patients were euthyroid (median 7.37 Hz) ($P > 0.05$).

Baseline tremor power showed a wide inter-patient variability ranging from $36\text{--}16390\text{ (mg}^2\text{ s}^{-1}\text{)}$ (median 234) when hyperthyroid and from $20\text{--}3052\text{ (mg}^2\text{ s}^{-1}\text{)}$ (median 95) when euthyroid but the difference between the

baseline tremor power in the two states was statistically significant ($P < 0.05$). In the hyperthyroid group there was a significant increase in median tremor power at 15 and 30 min ($P < 0.05$) after theophylline compared with baseline values (time 0) whereas no significant increase was seen after theophylline in the patients when euthyroid.

The area under the median tremor power-time curve was significantly lower in the euthyroid state compared with the hyperthyroid since theophylline produced a five-fold increase in maximum median tremor power in the hyperthyroid state compared with a non significant change in euthyroidism 30 min after theophylline administration ($P < 0.05$) (Figure 1). Plasma theophylline concentrations fell from $20 \pm 8.5\text{ mg l}^{-1}$ at 15 min to $3 \pm 1.3\text{ mg l}^{-1}$ at 7 h in the hyperthyroid state and from $22 \pm 6.4\text{ mg l}^{-1}$ at 15 min to $4.9 \pm 1.6\text{ mg l}^{-1}$ at 7 h when the patients were euthyroid (Figure 2). The pharmacokinetic variables are shown in Table 1. Plasma half-life of elimination of theophylline rose from $4.1 \pm 1.4\text{ h}$ in the toxic state to $6.1 \pm 2.0\text{ h}$ when euthyroid ($P > 0.01$). Plasma theophylline clearance fell from $3.9 \pm 1.1\text{ l h}^{-1}$ when hyperthyroid to $2.7 \pm 1.2\text{ l h}^{-1}$ in the euthyroid state ($P < 0.002$). Volume of distribution (V_{area}) in the hyperthyroid state was $21.6 \pm 4.0\text{ l}$ and

Figure 1 Median tremor power before (time 0) and after intravenous aminophylline (350 mg) in the hyperthyroid (●) and euthyroid (○) state. * indicate significant differences ($P < 0.05$) from baseline value.

Table 1 Pharmacokinetic variables for theophylline in six hyperthyroid subjects before and after treatment to euthyroidism

Patient	Sex	Age (years)	Weight (kg)	$t_{1/2}$ (h)	Hyperthyroid state	
					CL (l h ⁻¹)	V _{area} (l)
1	F	67	75.0	6.29	2.62	23.8
2	F	61	73.0	5.18	2.92	21.8
3	F	50	53.6	3.87	3.93	22.0
4	M	46	60.0	3.28	5.83	27.6
5	F	61	52.7	2.85	4.02	16.6
6	F	64	60.0	3.16	3.88	17.8
Mean				4.1*	3.9**	21.6
s.d.				1.4	1.1	4.0
Patient	Sex	Age (years)	Weight (kg)	$t_{1/2}$ (h)	Euthyroid state	
					CL (l h ⁻¹)	V _{area} (l)
1				8.92	1.91	24.6
2				7.16	2.07	21.4
3				6.17	2.31	20.6
4				3.28	5.09	29.8
5				4.64	2.85	19.0
6				6.46	2.04	19.0
Mean				6.1	2.7	22.4
s.d.				2.0	1.2	4.2

Significantly different from euthyroid state * $P < 0.01$,** $P < 0.002$. **Figure 2** Mean plasma theophylline concentrations after intravenous aminophylline (350 mg over 15 min) in the hyperthyroid (●) and euthyroid (○) state.

22.4 ± 4.2 l when euthyroid ($P > 0.05$). There was no significant relationship between FT_3 or FT_4 and theophylline clearance in either the thyrotoxic or euthyroid states and no relationship between the falls in FT_3 or FT_4 and the fall in theophylline clearance.

Discussion

The frequency of thyrotoxic tremor has been shown previously to be similar to physiological tremor (Lippold *et al.*, 1959; Marsden *et al.*, 1968). This study has confirmed this and also the increased tremor power in hyperthyroidism (Abila *et al.*, 1985).

Tremor is also an adverse effect of the xanthine derivatives used in the treatment of obstructive airways disease. Theophylline (1,3 dimethyl-xanthine) has been shown to increase finger tremor by up to 80% when given intravenously (Laursen *et al.*, 1984) having a peak tremor frequency within the range quoted for thyrotoxic tremor. We have shown a potentiation of the effect of aminophylline on finger tremor in hyperthyroidism. The potentiation was seen despite greater theophylline clearance in the thyrotoxic state, so a pharmacodynamic mechanism is therefore likely.

Vozeh *et al.* (1984) suggested that theophylline metabolism was related to free thyroxine (FT_4) rather than FT_3 concentration. They also showed a significant relationship between the fall in FT_4 and the fall in theophylline clearance. In a recent report in 19 asthmatic euthyroid

subjects receiving slow release theophylline preparation at steady state, it was also shown that theophylline clearance correlated with free thyroxine (FT₄) concentration (Williams *et al.*, 1987).

In this small study we could not find any significant relationship between the absolute FT₄ or FT₃ and theophylline clearance or between the change in thyroid hormone concentrations and change in theophylline clearance, possibly because the subject with the highest thyroid hormone concentrations and the largest fall after treatment (patient 2) had the second smallest theophylline clearance which changed only modestly when he was rendered euthyroid.

It is unclear whether the high thyroid hormone levels seen in thyrotoxicosis cause tremor by a direct effect or by modification of adrenoceptor tremor enhancing mechanisms and whether the effect is central in origin or in the periphery. It has certainly been suggested that there may be an increase in β -adrenoceptor population in a number of tissues and cells in hyperthyroidism (McConnaughey *et al.*, 1979; Ginsberg *et al.*, 1981) and that β -adrenoceptor blockers reduce thyrotoxic tremor (McDevitt & Nelson, 1978). It has also been proposed that thyroid hormones may regulate guanine nucleotide regulatory protein production at the adenosine receptor-adenylate cyclase complex (Stiles, 1986) with which adrenoceptors are closely related. This might alter the sensitivity of the adenylyl cyclase system to adenosine, although this re-

mains speculative. Short-term hyperthyroidism in the rat is associated with a reduction of inhibiting (A₁) adenosine receptors in fat cells, and this could also occur at other sites (Rapiejko & Malbon, 1987).

Methylxanthines affect many systems in the CNS (Cardinali, 1980) and a number of hypotheses have been suggested to explain their production of tremor. These include alteration in calcium uptake (Kolbeck *et al.*, 1977), prostaglandin antagonism (Horrobin *et al.*, 1977) and catecholamine release (Vestal *et al.*, 1983). However, the rise in plasma catecholamines after theophylline is small and unlikely to be responsible for the tremor (Warren *et al.*, 1983). Perhaps more important, however, is the possibility that xanthine tremor involves antagonism of the endogenous nucleoside, adenosine (Fredholm, 1980). Since the major neurophysiological action of adenosine is inhibitory (Phillis *et al.*, 1979) it is possible that methylxanthines exert their tremorogenic action by blocking inhibitory adenosine receptors linked to the enzyme adenylyl cyclase (Tolkovsky & Levitzki, 1978).

It is also therefore possible that altered adenosine responsiveness is associated with both hyperthyroid and theophylline-induced tremor, although further work is required to examine this suggestion.

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