A comparison of the CNS effects of enprofylline and theophylline in healthy subjects assessed by performance testing and subjective measures

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1 The effects of intravenous infusions of enprofylline, theophylline, and placebo on subjective ratings and on psychological test performance were studied in a double-blind crossover experiment in 12 healthy subjects who abstained from caffeine throughout the experimental procedures.

2 Mean plasma concentrations of enprofylline were: mean 2.9 mg l⁻¹ (range 1.9–3.4). Those for theophylline were: mean 12.1 mg l⁻¹ (range 9.0–14.4).

3 Performance on the auditory vigilance task showed a significant improvement with theophylline compared with both enprofylline and placebo. The correct detection rates (out of 90) were 50.3, 43.4 and 39.1 respectively. A similar effect was seen with finger tapping rates: 404, 394 and 390 taps min⁻¹ respectively. Other measures showed no significant effects, although choice reaction time showed a trend towards faster responses with theophylline.

4 Subjective ratings showed that subjects were significantly more alert with theophylline than with enprofylline. Subjects reported themselves as significantly more dizzy and ill with both active drugs compared with placebo.

5 These results suggest that enprofylline largely lacks the CNS stimulant effects of theophylline, but that the incidence of other unwanted effects of the drugs may be similar.

Keywords theophylline enprofylline vigilance visual analogue scales psychomotor performance

Introduction

One of the main problems with the use of xanthine bronchodilators such as theophylline is CNS stimulation, which can lead to restlessness, tremor, and sleep disturbance (Ellis, 1984; Rall, 1985). This stimulant effect, like that of caffeine, has been shown to be related to adenosine receptor antagonism (Spealman, 1988).

Enprofylline is a novel xanthine which, like theophylline has bronchodilator properties. However it lacks adenosine inhibition, and should therefore not show the CNS stimulant effects of other xanthines (Lunell *et al.*, 1983; Persson &

Kjellin, 1981). Such a difference could well be of clinical significance (Chapman *et al.*, 1990).

Theophylline is closely related to caffeine in its chemical structure, and its CNS effects are similar (Rall, 1985). There is a substantial literature on the various aspects of CNS stimulation with caffeine, for example its effects on mood, psychomotor performance, and sleep (Bruce & Lader, 1986). However relatively little work has been reported on theophylline, and most of this relates to children (see e.g. Rappaport *et al.*, 1989). The fact that theophylline and other

methylxanthines exert their CNS stimulant effects by the same mechanism suggests that it is appropriate to use measures known to show the CNS effects of caffeine in investigating other xanthines.

Previous studies have shown that the subjective effects of caffeine are readily demonstrated, but that objective measurement using tests of psychological performance is less straightforward. It seems that the clearest effects may be on attention or vigilance tasks of long duration, in which the stimulant effect is seen as a sustaining of performance, which declines in the absence of such stimulation (Bruce *et al.*, 1986; Fagan *et al.*, 1988).

In the present study, the stimulant effects of theophylline and enprofylline were compared with placebo in healthy volunteers. The main objective measure used was the auditory vigilance task of Wilkinson (1968), which lasts 1 h, and which has been previously shown to be sufficiently sensitive to detect 200 mg caffeine (Fagan *et al.*, 1988). Other standard performance tests were included, as it is always desirable to assess a broad range of abilities in this type of study. Subjective assessment used a range of visual analogue scales. Previous work suggested that a stimulant effect would be shown by an increase in alertness, and possibly by a reduction in boredom (Bruce *et al.*, 1986; Fagan *et al.*, 1988).

Drugs were administered as intravenous infusions, with plasma concentrations targetted at therapeutic levels. Giving drugs in this way has the advantage that steady-state levels can be rapidly achieved, and the problems of interpreting test results obtained while drug concentrations are rapidly changing are avoided.

Methods

Twelve healthy male subjects, aged 18–40 years, took part in the study. Subjects were judged normal on an initial screening which included clinical examination, haematology, biochemistry, urinalysis and resting ECG. No subject was taking any medication. Written informed consent was obtained. The study was approved by the ethics committee of the Royal Infirmary, Edinburgh.

The study used a three-period crossover design, in which subjects received intravenous infusions of enprofylline, theophylline or placebo. The order of administration was randomised using a Latin square, and the study was carried out double-blind. At least 7 days elapsed between sessions.

The following measures of performance were used:

Auditory vigilance task

The subject listened through headphones to a series of tones, against a background of white noise. Most of the tones were 500 ms duration, but one in 20, at random, was only 400 ms long. The subject's task was to press a button whenever he heard a short tone. A total of 1800 tones was presented. The test lasted 1 h (Fagan *et al.*, 1988; Wilkinson, 1968).

Continuous attention task

A series of geometric patterns was flashed on a screen, each pattern being shown for 0.1 s, the interval between patterns being 1.5–2.5 s. The subject's task was to respond whenever two consecutive patterns were the same. A total of 240 presentations, with 40 repetitions, was used in each test (Tiplady, 1985, 1988). The total number of errors (both false-positive and false-negative) was recorded, and the error index calculated (Pigache, 1976).

Critical flicker fusion threshold

The subject observed a group of four lights which flickered at an increasing frequency. The subject responded when the lights appeared to be steady. The test was then repeated in the opposite direction. The mean of three observations in each direction was taken as the threshold (Hindmarch, 1975).

Choice reaction time

This used an apparatus with six buttons arranged in a semi-circle by each of which was a light. The subject initially placed his finger on a seventh button at the centre of the semi-circle. At random intervals one of the lights was illuminated, whereupon the subject responded by pressing the appropriate button as quickly as possible. The mean latency and total response time over 30 responses was taken (Frewer & Hindmarch, 1988; Hindmarch, 1975).

Visual vigilance task

The subject observed a constantly changing random pattern of dots on a monitor screen. At intervals a square pattern gradually appeared in one quarter of the screen. The subject pressed one of four buttons to indicate the position of the pattern as soon as he was able to detect it. The total number of correct and incorrect responses in 10 min was recorded.

Tapping test

The subject tapped with the index finger of the preferred hand on a morse key as fast as he could for 1 min.

Gibson spiral maze

In this pencil-and-paper test, the subject drew around a spiral path, without touching the sides of the maze nor the obstacles in the path, as quickly as possible. Completion time and number of errors were recorded (Gibson, 1977).

Digit-symbol substitution test

In this pencil-and-paper test, there was a key which matched nine symbols to the numbers 1–9. A series of random numbers was printed in a grid on the sheet, and the subject wrote the corresponding symbol under each number, as fast as possible. The number of correct and incorrect symbols written in 90 s was recorded (Wechsler, 1958).

Visual analogue scales

Subjective effects were measured using five visual analogue scales the opposite ends of which were marked: Alert–Drowsy; Steady–Dizzy; Calm–Tense; Interested–Bored; Well–Ill. Non-specific questioning was also used ('How do you feel at the moment'), and any symptom or other item reported was rated on a 7-point severity scale.

Procedures

Each subject first took part in four practice sessions in which all tests were performed once. At the first practice, the auditory vigilance test was introduced using a series of short runs in which the difference between long and short tones was greater than in the standard test. The difficulty of discrimination was then gradually increased. The subsequent three practice sessions used the standard test. The four practice runs were spread over at least 2 days.

Subjects were instructed to abstain from caffeine-containing beverages for a period starting one week prior to the first main session, and continuing until the completion of all test procedures. Decaffeinated coffee was provided *ad libitum*. Use of tobacco was not allowed from 18.00 h on the day preceding the tests until the end of the day's testing. For alcohol there was a similar restriction, but from 24 h preceding the test day.

In each of the main sessions, a blood sampling

cannula (18G Venflon) was inserted into the antecubital fossa of the left arm. A smaller cannula (21G Venflon) was inserted into a vein on the right forearm, and was connected via flexible nylon tubing to the infusor pump. The cannula and tubing, were arranged to allow freedom of movement of the right arm. A tap was fitted into the lines behind the right shoulder to control infusion. The pump and connections were behind the subject so that the starting time of the infusion would not be known by the subject.

An infusion of saline was started for all subjects, who then completed all the tests with the exception of the auditory vigilance test in the following sequence: visual analogue scales; continuous attention task; tapping; critical flicker fusion; choice reaction time; visual vigilance task; digit-symbol substitution; Gibson spiral maze. They then received theophylline, enprofylline or placebo as follows. Theophylline: loading dose of 5 mg kg⁻¹ in 30 min, followed by a maintenance infusion of 0.025 mg kg⁻¹ min⁻¹; enprofylline: loading dose of 1.5 mg kg⁻¹ in 30 min, followed by a maintenance infusion of 0.015 mg kg⁻¹ min⁻¹; placebo: saline given in the same volumes, and with the same procedures as for the active drugs. The total duration of each infusion was 2.5 h.

Thirty minutes after the commencement of the maintenance infusion, subjects completed the full test battery. The order of tests was the same as above, except that the visual analogue scales were administered at the end as well as at the beginning, and the auditory vigilance test was included after the visual vigilance. During the whole test period, non-specific questioning was made at approximately 10 min intervals, except when testing was in progress.

Plasma drug concentrations

Blood samples for estimation of theophylline and enprofylline were taken during the saline infusion and at 1 and 2.5 h after the start of the maintenance infusion. Assay was by means of column liquid chromatography as described by Ögren & Österlind (1984).

Statistical analysis

The Friedman analysis of variance was used to determine overall significance for each objective and subjective measure. For the subjective measures, the means of the two ratings during infusion (at 1 and 2.5 h approximately) were analysed. Where significant differences among treatments were found, this was followed by pairwise comparisons to assess the individual

differences. The critical level of significance used was $P < 0.05$.

Results

The results from the performance tests are presented in Table 1. Of the measures studied, only the auditory vigilance test and tapping showed statistically significant differences among treatments ($P < 0.05$). In both cases theophylline showed improved performance compared with the other two treatments—a higher number of correct responses for the vigilance test, and a faster rate of tapping. Errors on the vigilance test showed no discernible change.

Data from the visual analogue scales are shown

in Figure 1. Subjects reported themselves as less drowsy on theophylline than on enprofylline (alert-drowsy: $P < 0.05$); as more tense on theophylline than on placebo (tense-calm: $P < 0.01$) and as more dizzy and ill on both active compounds than on placebo (steady-dizzy: $P < 0.01$; well-ill: $P < 0.001$).

Symptoms reported by the subjects in response to non-specific questioning are shown in Table 2. Although the number of subjects reporting symptoms is too small to show statistical significance, there is a clear trend for more symptoms to occur with the active compounds, the commonest symptoms being headache and nausea. One subject vomited during the enprofylline session.

The plasma concentrations of enprofylline

Table 1 Results from the performance measures with intravenous infusion of saline (P), enprofylline (E) or theophylline (T). Data are shown as mean (s.d.)

	P	Before infusion E	T	P	During infusion E	T
<i>Continuous attention task</i>						
Number correct	32.0 (4.0)	31.6 (8.1)	31.3 (6.4)	32.1 (5.8)	31.1. (6.9)	33.8 (5.2)
Number incorrect	0.75 (0.62)	1.00 (1.21)	0.92 (1.31)	1.00 (1.28)	0.83 (1.70)	0.33 (0.89)
Error index	0.21 (0.10)	0.22 (0.21)	0.23 (0.16)	0.21 (0.15)	0.23 (0.18)	0.16 (0.13)
<i>Auditory vigilance test</i>						
Number correct	—	—	—	39.1 (13.9)	43.4 (16.8)	50.3 (15.9)*
Number incorrect	—	—	—	9.4 (8.4)	10.2 (8.1)	9.3 (10.7)
<i>Visual vigilance task</i>						
Number correct	38.8 (6.4)	37.2 (5.3)	38.0 (5.8)	38.9 (5.4)	38.7 (5.4)	38.8 (5.3)
Number incorrect	0.08 (0.29)	0.17 (0.39)	0.33 (0.49)	0.33 (0.49)	0.17 (0.39)	0.25 (0.62)
<i>Choice reaction time (ms)</i>						
Latency	386 (54)	395 (85)	382 (46)	377 (47)	379 (61)	364 (36)
Motor time	192 (75)	164 (54)	163 (23)	169 (59)	175 (55)	153 (24)
Total time	578 (120)	558 (130)	545 (60)	546 (88)	554 (99)	517 (44)
<i>Critical flicker fusion threshold (Hz)</i>						
Frequency	29.1 (4.2)	29.3 (3.5)	28.9 (4.3)	29.2 (3.6)	28.5 (3.6)	28.8 (3.9)
<i>Gibson spiral maze</i>						
Time (s)	17.9 (4.1)	18.1 (4.6)	18.3 (3.9)	18.0 (4.4)	18.5 (4.5)	18.3 (3.5)
Errors	14.3 (7.1)	12.7 (6.0)	12.4 (6.4)	13.7 (6.6)	12.9 (6.9)	11.5 (5.4)
<i>Digit-symbol substitution</i>						
Number correct	70.5 (9.9)	69.4 (11.0)	69.7 (10.8)	69.0 (8.5)	67.6 (11.8)	68.7 (9.4)
<i>Tapping</i>						
Number min ⁻¹	405 (39)	402 (33)	397 (33)	390 (39)	394 (36)	404 (35)*

*Theophylline significantly differs from enprofylline and placebo ($P < 0.05$ on Friedman ANOVA and on pairwise comparisons). No statistically significant difference between enprofylline and placebo.

Figure 1 Subjective effects of xanthines as assessed by visual analogue scales. Data are mean positions on the line in mm. Increases represent changes in the direction of the named extremity of the scale. □: theophylline; ▲: enprofylline; —: placebo.

and theophylline 1.5 and 2.5 h after the start of the infusion are shown in Figure 2. The mean concentrations of the 1 and 2.5 h time points were calculated. These were in the range 1.9–3.4 mg l⁻¹ (mean 2.9) for enprofylline and 9.0–14.4 mg l⁻¹ (mean 12.1) for theophylline. There was a clear trend for an increase in concentrations with time. The mean increase was 6.5% for the enprofylline session (range -5.3%–+18.9%) and 1.1% for the theophylline session (range -8.6%–+5.9%).

Discussion

These results provide clear evidence for the CNS stimulant effect of theophylline. The auditory

Table 2 Incidence of symptoms reported during infusion, as elicited by non-specific questioning

Symptom	Placebo	Theophylline	Enprofylline
Headache	1,3	1,2	1,2,2
Nausea	4	1	1,3,4
Alert		4,4	
Shaky		2	4
Sweaty		2	3
Tremor		1	2
Jittery		1,1	
Vomiting			4
Muscle tension		4	
Dizzy			2
Twitching		1	
Pallor			1
Drowsy			1

Each number represents the maximum severity reported for a single subject. Thus two subjects reported headache on placebo, one with maximum severity 1, the other with maximum severity 3. One subject reported nausea on placebo, with severity 4.

Figure 2 Plasma concentrations of enprofylline (a) and theophylline (b). Thin lines: individual values; thick lines: mean concentrations.

vigilance test, the objective measure identified as capable of showing acute effects of caffeine in previous studies, showed statistically significant effects in the predicted direction of increased correct detection compared with placebo. Finger tapping rate also showed an increase, as has been shown in some but not all studies with caffeine (Bruce *et al.*, 1986; Cluble *et al.*, 1979; Fagan *et al.*, 1988). There was also a significant effect for alertness, although it should be noted that in this case only the pairwise comparison for theophylline vs enprofylline attained significance, while that for theophylline vs placebo did not ($0.05 < P < 0.1$).

By contrast, no effects of enprofylline were apparent in the objective measures, supporting the suggestion that this drug largely lacks the CNS stimulant effects associated with other xanthines.

Two established pencil-and-paper tests (Gibson spiral maze and digit-symbol substitution) and a new automated vigilance test (the visual vigilance task) were included in the present study. These are known to be capable of detecting sedative drug effects (for example nitrous oxide, Fagan, in preparation), and it was considered possible that they might be capable of showing improvement with theophylline as none has an obvious ceiling effect. This proved not to be the case however, supporting the suggestion made previously that tests of long duration are in general necessary to detect stimulant effects (Bruce *et al.*, 1976; Fagan *et al.*, 1988).

No significant change was here observed with the interested-bored analogue scale, although the trend was similar to that seen with alertness. The remaining scales showed a different pattern, however. With both enprofylline and theophylline, subjects reported themselves as significantly more dizzy, and ill. This may reflect the known potential of both enprofylline and theophylline to produce nausea (see e.g. Chapman *et al.*, 1990; Laursen *et al.*, 1984), and taken together with the adverse events reported here suggest that apart from CNS stimulation, the two drugs may have similar profiles of unwanted effects.

The therapeutic window for theophylline is considered to be 10–20 mg l⁻¹, and that for enprofylline approximately four times lower (Laursen *et al.*, 1984). Infusion rates were selected to maintain plasma concentrations within the lower part of this range. The data shown in Figure 2 show that this was largely achieved, in

that 10 of the 12 subjects showed mean plasma concentrations above 10 mg l⁻¹ theophylline or 2.5 mg l⁻¹ enprofylline. There was a clear trend for increasing concentrations over the time course of the infusion, but this was small, and unlikely to have a perceptible effect on the results. The ratio of the mean concentrations of theophylline/enprofylline was 4.2, suggesting that doses were close to equipotent in terms of bronchodilator effect. Thus the differences in performance effects would seem to reflect the differing profile of the two drugs.

A limitation of the present study is that it uses only acute measures, and studies with longer term administration in volunteers or patients are desirable to assess the clinical significance of these findings. There are problems with such work, however. If subjects' sleep is disturbed, performance on subsequent days may be impaired. Thus stimulant drugs may cause impairment rather than improvement in performance with long-term administration. Moreover, in patients, effective treatment may reduce sleep disturbance due to the symptoms of asthma, thus adding a further possible source of confounding. The acute, volunteer study is therefore important as a starting point, giving data that may be relatively easily interpreted in terms of CNS stimulation.

In conclusion, these results support the suggestion that enprofylline largely lacks the CNS stimulant effect of other xanthines, and suggests that development of an effective xanthine bronchodilator with fewer unwanted effects than theophylline may be possible.

We thank AB Draco, Lund, Sweden, for carrying out the assays of enprofylline and theophylline.

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(Received 5 January 1990,
accepted 5 March 1990)