Pharmacokinetic and pharmacodynamic responses to caffeine in poor and normal sleepers

Abstract Pharmacokinetic and pharmacodynamic responses to caffeine (2.5 mg/kg) were compared between ten healthy self-rated poor sleepers and ten normal sleepers. Sleep pattern assessed by the Pittsburgh Sleep Quality Index (PSQI). There was no significant difference in mean estimated daily caffeine consumption between the groups. The poor sleepers had significantly higher scores for neuroticism on the Eysenck Personality Questionnaire (EPQ) and anxiety on the Hospital Anxiety Depression (HAD) scale, compared with normal sleepers. Caffeine pharmacokinetics were assessed by measurement of saliva caffeine concentrations. Poor sleepers showed significantly greater variability in caffeine C_WRAPorate max, clearance and half-life, compared to normal sleepers. Pharmacodynamic measures included heart rate, blood pressure, visual analogue scales for concentration, vigilance and relaxation, psychomotor performance [Digit Symbol Substitution Test (DSST) and tapping rate (TR)] and EEG activity [Contingent negative variation (CNV), auditory evoked potential and power spectral analysis]. Prior to caffeine administration, poor sleepers compared to normal sleepers had faster heart rates, lower ratings for concentration and relaxation, poorer performance on the DSST, greater CNV magnitude, faster peak alpha frequency and lower delta, theta and beta power. These differences persisted after caffeine ingestion and overall differences between the groups on these measures were significant ($P < 0.01$–$0.001$). Post-dose, but not pre-dose, scores for vigilance and TR were significantly lower overall in poor compared with normal sleepers. Despite the baseline differences between poor and normal sleepers, the changes following caffeine administration were similar in direction and magnitude in both groups.

Key words Insomnia • Caffeine • Pharmacokinetics • Pharmacodynamics

Introduction

A considerable number of otherwise healthy individuals complain of poor sleep. The prevalence of subjective insomnia in adults has been estimated to be as high as 35% (Dorsey 1991) and there is growing concern that daytime sleepiness resulting from insomnia increases the risk of industrial, traffic, and other accidents (National Institute of Mental Health 1984; Balter and Uhlenuth 1992). It seems possible that caffeine, an almost universally consumed central nervous system stimulant drug, might contribute to this symptom. There is some evidence that subjects who attribute their poor sleep to caffeine have a prolonged elimination half-life of this drug (Levy and Zylber-Katz 1983) and several studies have suggested that patients with anxiety disorders have an increased sensitivity to the stimulant and anxiogenic effects of caffeine (Greden 1974; Boulenger and Uhde 1982; Boulenger et al. 1984; Charney et al. 1985; Bruce et al. 1992). The present study investigated pharmacokinetic and pharmacodynamic responses to caffeine in a group of self-rated poor sleepers compared with a group of normal sleepers.

Materials and methods

Subjects

Twenty unpaid volunteers were recruited for the study by newspaper advertisement and included ten subjects who considered themselves to be poor sleepers and ten normal sleepers matched for age and sex; all subjects were white caucasians. In each group there...
were five males and five females. The mean age (± SD) of the poor sleepers was 37.3 years ± 11.2 years (median 38.5 years) and that of the normal sleepers was 34.4 ± 12.6 years (median 30.5 years). All subjects were healthy non-smokers; none had a psychiatric history or were taking psychotropic medicines; none of the females were taking oral contraceptives. Haematology, serum biochemistry and full liver function tests were performed prior to the start of the study and the results were normal in all participants. The project was approved by the joint Newcastle Health Authority/University of Newcastle upon Tyne Ethics Committee and volunteers gave informed consent.

Measurements and procedures

At an initial interview, sleep pattern for each subject was assessed by the Pittsburgh Sleep Quality Index (PSQI) (Wolstein et al. 1983; Berman et al. 1988). Personality characteristics were determined by the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck 1975) and the Hospital Anxiety Depression (HAD) scale (Zigmond and Snaith 1983) was used to assess state anxiety and depression. Caffeine consumption was evaluated by a questionnaire which recorded usual daily consumption of tea, coffee (filter and instant), chocolate drinks or foods, and usual time of day at which each was consumed. An approximate estimate of daily caffeine consumption was calculated using the following caffeine values: instant coffee 85 mg/cup; filter coffee 100 mg/cup; tea 65 mg/cup; decaffeinated coffee 3 mg/cup; cola 18 mg/6 fl oz; cocoa 4 mg/cup; chocolate 1 mg/g (Barone and Roberts 1984; James and Crosby 1987; James 1991).

One or 2 weeks later, volunteers attended a morning laboratory session after fasting overnight and abstaining from caffeine and alcohol for 24 h. In this session, responses to a single oral dose of caffeine (2.5 mg/kg caffeine administered as caffeine citrate in a capsule) were measured. Caffeine pharmacokinetics were followed by measurement of saliva caffeine concentrations. Saliva (3 ml) was collected by spitting directly into plastic vials. The samples were obtained immediately prior to caffeine dose, and at 15, 25, 45, 55, 75, 105, 135, 195, 240, 360 and 480 min post-dose. A light meal was provided at 180 min post-dose.

Saliva concentrations of caffeine were measured using the reverse-phase HPLC method of Badcock et al. (1990). The coefficients of variation of replicate analysis of samples containing 2.5, 5 and 10 µg ml⁻¹ were 13.15, 11.47 and 11.48%, respectively.

Measurement of caffeine pharmacokinetics

Caffeine concentration-time area under the curve (AUC) was determined by the linear trapezoidal rule. Caffeine half-life (t1/2) was calculated by least squares regression analysis. Caffeine clearance (CL) was calculated by CL = dose/AUC. Time to maximum concentration (tmax) and maximum saliva caffeine concentration (Cmax) were determined by visual inspection of the data.

Pharmacodynamic responses

Responses to caffeine were assessed by measurements of cardiovascular function, subjective ratings, psychomotor performance, and EEG. Heart rate and blood pressure were recorded by autosphygmanometer at each saliva sampling time; all the other measurements were made at 30 min and immediately prior to the caffeine dose, and at 30-min intervals post-dose for 4 h. Subjective ratings of concentration, vigilance and tension/relaxation were obtained by visual analogue scales (VAS) between the extremes: “Wonderfully alert and penetrating mind – Extremely difficult to concentrate”, “Marvelously alert and energetic – Awfully sleepy and lackluster”, and “Utterly relaxed and tranquil – Terrible agitation” respectively. Psychomotor performance was assessed by the Digit Symbol Substitution Test (DSST) and tapping rate (TR).

Electroencephalographic (EEG) activity was recorded from silver/silver chloride gel-filled scalp electrodes. The output was amplified (Biodata PA400 amplifier system) and interfaced via an IEEE 488 located in a Nimbus 386 DX microcomputer to a computerised EEG data acquisition and analysis package. Two evoked potentials, the contingent negative variation (CNV) (Walter et al. 1964) and the auditory evoked potential (AEP) (Shagass and Straumenis 1978, Pritchard 1981), and power spectrum analysis of background EEG frequencies (Fink 1978) were measured.

The evoked potentials were recorded between vertex and linked mastoid sites with compensation for eye movements recorded from nasion-linked mastoid electrodes (Cooper et al. 1980). For the CNV, subjects were presented through earphones with a series of ten paired signals: a “warning” tone, S1 (1000 Hz, 200 ms, 60 db) and an “imperative” tone, S2 (650 Hz, 400 ms 60 db) to which they were required to respond by pressing a button. The S1-S2 interval was 1.25 s, but the intervals between signal pairs were varied randomly between 6 and 10 s. The response to the ten signal pairs was averaged and the CNV was calculated as the area of negativity between S1 and S2 and expressed in µVs. Reaction time (RT) for each S1 signal was recorded on a digital counter which was activated by S0 onset and stopped by the subject pressing the button. Mean RT for each series of ten signal pairs was calculated.

For the AEP, a sequence of 120 tones were presented every 1.5 s in an "oddball" paradigm consisting of 100 frequent tones (1000 Hz, 200 ms, 60 db) and 20 randomly inserted rate tones (650 Hz, 200 ms, 60 db). Subjects were required to fix their attention on and count mentally the number of low tones in each sequence. The responses to the frequent and rare tones were analysed separately and calculated as amplitude (µV) and latency (ms) of the late components N1, P2, N2 and P200. Subtraction of the averaged responses to the rare and frequent tones also allowed visualisation and calculation of the peak to peak amplitude of the N2, P200 component which typically appears in response to the rare tones.

Power frequency spectrum was calculated by fast Fourier transform of the average of 25 2 s-epochs of resting EEG activity (eyes open and eyes closed) recorded from a left occipital-linked mastoid electrode and expressed as µV²·µHertz, in each frequency band: delta (0-4 Hz), theta (5-7 Hz) alpha (8-12 Hz), beta (13-35 Hz). Peak alpha frequency was also measured.

Data analysis

The Students’ t-test was used for comparisons of data which appeared to be normally distributed. Normality was tested for by producing a Normal plot and using a Ryan-Fourier Test. The Mann-Whitney U test was used if the data did not conform to a normal distribution. Individual measurements were summarised for the purpose of intergroup comparisons over time as recommended by Matthews et al. (1990). Such comparisons included between group means at each measurement time and mean overall response determined by calculation of area under the curve (AUC 0-4 h).

Results

Pittsburgh Sleep Quality Index (PSQI)

This questionnaire has seven elements, each scored on a four point scale from 0 = the best sleep to 3 = the worst sleep; scores are added to give a global sleep score (GSS). Normal sleepers had a mean ± SD GSS of 3.0 ± 1.5, while poor sleepers had a GSS of 13.4 ± 4.0