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Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers

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1 The effects of simvastatin and pravastatin on measures of central nervous system activity were investigated in a double-blind, placebo-controlled, randomised crossover study.
2 Twenty-five healthy volunteers sequentially took 40 mg day^{-1} simvastatin, 40 mg day^{-1} pravastatin or placebo for 4 weeks, separated by a 4–6 week washout phase.
3 CNS measures included EEG evoked potentials, power spectral analysis, Leeds Sleep Questionnaire, Hospital Anxiety Depression (HAD) Scale, and Digit Symbol Substitution Test (DSST); biochemical measures included plasma cholesterol, liver enzymes (γ-GT, AST, ALT) and creatine kinase.
4 Mean cholesterol concentrations with both drugs were significantly lower than with placebo, and the cholesterol-lowering effect was greater with simvastatin. There were no significant differences between treatment in EEG evoked potentials, HAD Scale, or DSST scores. On the sleep measure, subjects reported significantly greater difficulty in getting to sleep while on simvastatin than on pravastatin, but neither score differed from placebo. No significant correlations were observed between sleep ratings and either plasma cholesterol concentrations or EEG evoked potentials.
5 The study showed that, while both drugs reduced plasma cholesterol concentrations, neither exerted significant effects, compared with placebo, on EEG evoked potentials, mood, sleep, or cognitive performance after 4 weeks of chronic administration in healthy volunteers.

Keywords simvastatin pravastatin cholesterol EEG depression

Introduction

Several recent reports have suggested a linkage between cholesterol lowering and mortality from non-cardiac causes [1, 2]. The most prominent of these causes include violent deaths such as suicide and accident. There is considerable doubt concerning the reality of such an association, when other risk factors for violent death are taken into account [3–5] and it is far from clear whether or not any linkage is causal. However, some studies have shown an increased rate of suicide [6], alcohol-related diseases [7] and depression [8] in subjects with low plasma cholesterol levels. A suggested mechanism is that lowered plasma cholesterol concentration could cause alterations in central transmitter function leading to depression [9]. An alternative possibility is that agents used to lower serum cholesterol may directly affect brain function themselves.

HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors are becoming established in the treatment of primary hypercholesterolaemia. Of the two principal HMG CoA reductase inhibitors one, simvastatin, is much more lipid soluble than the other, pravastatin (see for example Brown & Goldstein [10]). One might expect simvastatin to enter the CNS more readily and indeed reports of sleep disturbance have been reported more frequently with this agent compared with pravastatin, suggesting a possible direct action on the CNS [11].

In this study simvastatin and pravastatin were compared in a double-blind, placebo-controlled protocol in an attempt to demonstrate direct or indirect effects of these agents on the CNS. The chief measures chosen for detecting any central drug effects were EEG variables:

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cortical evoked responses and power-spectral analysis. Of the evoked potentials, the contingent negative variation (CNV) has been shown to be exquisitely sensitive to centrally acting drugs including stimulants and depressants at doses below those required to produce subjective effects. For example, 20% changes in CNV magnitude are seen after a single dose of 2.5 mg nitrazepam, 300 mg caffeine and cigarette smoking [12, 13]. Furthermore the CNV has been shown to be altered by changes in attention and mood and to be reduced in depression [14]. Auditory evoked potentials (AEPs) are also altered by changes in attention and by psychoactive drugs [15] and in some people who attempt suicide [16]. In addition, various psychoactive drugs cause changes in background EEG frequency and amplitude, especially in the alpha (8–13 Hz) and beta (14–22 Hz) wavebands [17]. These objective measures of brain activity were supplemented in the current study by subjective measures of sleep quality [18], anxiety and depression [19] and by a test of cognitive performance [20].

It was postulated that pravastatin would cause no significant alteration in any of these measures by virtue of its non-penetration of the CNS. Simvastatin might cause detectable effects if it possessed direct CNS activity.

Methods

Subjects

Twenty-five healthy volunteers (17 male, 8 female), average age 23.8 years (range 20.0–31.5) were included in the study. Exclusion criteria included history of cardiovascular, renal or hepatic impairment, positive personal or family psychiatric history, significant abnormality on physical examination or evidence of depression on the Beck Depression Inventory. In addition, a range of physical investigations were performed, including ECG and pregnancy test to identify subjects who might be unsuitable to enter the trial. Finally, volunteers taking concomitant medication which might affect EEG recordings or blood lipid levels were excluded. This included a restriction on alcohol to 10 units per week and on smoking to 10 cigarettes per day.

Measures

Evoked potentials The CNV was measured between vertex and linked mastoid sites with compensation for eye movement artefacts [21]. Subjects were presented with a series of ten paired signals: a short 'warning' tone S_1 (1000 Hz, 200 ms) and a longer 'imperative' tone S_2 (650 Hz, 400 ms) to which they responded by pressing a button. S_1–S_2 intervals were 1.25 s with intervals between signal pairs varying randomly between 6 and 10 s. Recordings were amplified through Biodata PA 400 amplifiers with a time constant of 10 s and low pass filter 30 Hz. Output was fed into an Apricot Xen computer programmed to average the response to ten pairs of signals and calculate the CNV area in μVs.

The post imperative negative variation (PINV) following each CNV was calculated as the area of negative variation measured for 1.25 s from 250 ms after S_2 (in μVs) [14].

Auditory evoked potentials (AEP) were recorded from the same electrodes as the CNV. Stimuli consisted of a series of 30 tones (1000 Hz, 60 dB, 200 ms) administered through headphones at randomly varied intervals of 8–12 s. Peaks N_1 and P_2 were identified and the mean N_1P_2 amplitude measured in μV. In addition the Root Mean Square [22–24] of the AEP was calculated as the square root of the mean of the square of the deviation of the waveform from the baseline in the time window 0–250 ms post-stimulus.

Power spectral analysis Background EEG activity was measured with eyes open and eyes closed from an occipital electrode (O_1) referenced to linked mastoid electrodes. Signals were amplified by using Biodata PA 400 amplifier (high pass filter 0.2 s; low pass filter 30 Hz; range 100 μV) connected to a Biodata Microlink 3 and Apricot Xen computer.

EEG activity was recorded in two cycles, one with eyes open and one eyes closed. Each cycle acquired 25, 2 s epochs and averaged spectra were computed off-line using Fast Fourier Transform (Biodata Software) for spectral analysis. EEG power (μV^2/Hz) was analysed in the frequency bands delta (0–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–13.5 Hz), slow beta (14.0–25.5 Hz) and fast beta (26.0–40.0 Hz) with a resolution of 0.5 Hz. The spectral difference index between the two cycles was also calculated.

Leeds Sleep Questionnaire A modified version of the questionnaire [18] was used. In addition to the standard questionnaire three further visual analogue scales were added with axes of more/less dreaming, more/less vivid dreams and more/less pleasant dreams.

Hospital Anxiety Depression Scale [19] This scale has ratings for both anxiety and depression. The Beck Scale for depression [25] and the Eysenck Personality Questionnaire [26] were also administered on the first visit.

Cognitive performance This was assessed by the digit symbol substitution test (DSST) [20].

Biochemical tests Subjects were regularly monitored for the following biochemical measures: blood sodium, potassium, calcium, phosphate, urea, creatine kinase, γ-GT, AST, ALT, glucose, urate, cholesterol and urinary protein.

Haematological tests Regular assays of haemoglobin, haematocrit, red and white cell counts and platelets were performed.

Experimental procedure

After 2 weeks placebo lead-in phase each volunteer sequentially took pravastatin 40 mg day^{-1}, simvastatin 40 mg day^{-1} or placebo in separate 4 week treatment phases in a crossover design of randomised order. Each treatment phase was separated by a 4–6 week washout

phase in which placebo was taken. Drugs were administered in the morning so that measurements were performed at the time of maximal blood concentration. Volunteers were blind at all times to which medication they were receiving. Investigators were blind to drugs administered during the treatment phases but not the placebo washout phases. Compliance was monitored by a tablet count at the end of each phase.

Immediately before each 4 week treatment phase all of the above measures, except the EEG recordings, were performed. Women volunteers were also given a pregnancy test. At the end of the treatment phases all measures, including EEG were performed. Prior to measurements subjects had been fasting for 12 h and had abstained from alcohol for 24 h. All measurements were made blind to the drugs received.

Repeated checks were made for significant adverse effects during the trial.

Statistical analysis

The above measures were compared in subjects when they were taking pravastatin, simvastatin or placebo. Analyses were made on the basis of a Jones and Kenward type formulation [27] for cross over trials and considered subject, period, direct treatment and carry over effects. Correlations were sought between EEG measures, cholesterol concentrations and sleep questionnaire parameters using the product-moment correlation coefficient. *A priori* statistical calculations predicted detection of the following between differences (significance level 0.05, power 0.9): root mean square AEP 1.9 μV, AEP 1.9 μV, CNV 2.1 μVs.

Ethical approval

Ethical approval was obtained from the Joint Ethics Committee of Newcastle upon Tyne.

Results

Compliance

Compliance, as assessed by tablet counts, was not significantly different between treatment groups. Average compliance (as a percentage) and standard deviations were simvastatin 95.3 ± 6.4, pravastatin 92.4 ± 9.4, placebo 96.4 ± 6.4.

EEG recordings (Table 1)

Adequate evoked potential and background EEG recordings were made from all subjects. No significant differences in evoked potential data were found between measures taken while on placebo, simvastatin or pravastatin (Table 1). In addition, no differences were shown in background EEG activity between treatments or placebo.

Table 1 EEG parameters of 25 subjects after 4 weeks treatment on simvastatin, pravastatin and placebo

	Pravastatin	*Simvastatin*	*Placebo*
CNV (μVs)	8.8 (6.7–10.9)	8.4 (6.4–10.3)	8.4 (6.2–10.7)
PINV (μVs)	1.7 (1.2–2.3)	1.7 (1.2–2.2)	2.5 (1.2–3.8)
AEP (μV)	24.9 (21.4–28.4)	25.3 (21.6–29.1)	25.1 (21.7–28.6)
RMS (μV)	19.1 (15.3–22.9)	17.7 (14.3–21.1)	19.0 (15.7–22.2)

No background EEG variables showed significant differences. Figures are expressed as means (95% confidence intervals).

Leeds Sleep Questionnaire

On the 100 mm visual analogue scale concerning difficulty in getting to sleep on drug compared with the pre-drug situation, subjects on placebo rated no difference from the pre-drug condition (mean (95% CI) = 50.1 (46.4–53.8): a score of 50 indicates that it is neither harder nor easier to get to sleep on drug treatment compared with pre-drug). The rating for subjects taking simvastatin was in the direction of 'more difficult to get to sleep' (47.0 (44.9–49.1)) while during pravastatin phase the rating was in the direction of 'less difficult to get to sleep' (51.4 (48.4–54.6)). The differences were small and ratings of either drug did not differ significantly from placebo. However, there was a significant difference between the two drugs ($P = 0.05$) with subjects on simvastatin apparently finding it 'more difficult to get to sleep' than when they were taking pravastatin. However, a similar question concerning time taken to fall asleep showed no drug effects. Similarly, no drug effects were noted on supplementary questions regarding dream frequency, vividness or pleasantness.

Hospital Anxiety and Depression Scale and DSST (Table 2)

No subject complained of anxiety or depression during the trial and none had scores on the Hospital Anxiety and Depression Scales suggestive of these diagnoses. There were no significant differences between treatment groups.

The Digit Symbol Substitution test showed a learning effect during the course of the trial. No treatment effects were found.

Biochemical tests

Mean cholesterol concentrations were significantly different between all three treatment phases with simvastatin exhibiting a greater lowering effect than pravastatin. Mean values after 4 weeks of treatment were simvastatin 3.85 (3.52–4.19) mmol l^{-1}, pravastatin 4.28 (3.93–4.63) mmol l^{-1} and placebo 5.02 (4.64–5.40) mmol l^{-1}, (Significance of differences: simvastatin/placebo, $P = 0.0001$; pravastatin/placebo, $P = 0.0079$; simvastatin/pravastatin, $P = 0.087$ NS.) Over the 4 week treatment phases mean changes in cholesterol levels with each drug were as follows: simvastatin −1.00 (−0.69 to −1.31) mmol l^{-1}, pravastatin −0.54 (−0.76 to −0.34) mmol l^{-1}, placebo −0.08 (−0.23 to +0.07)

Table 2 Sleep, HAD and DSST parameters of 25 subjects after 4 weeks treatment on simvastatin, pravastatin and placebo

	Pravastatin	*Simvastatin*	*Placebo*
Leeds Sleep Questionnaire (Hard to sleep score) (mm)	51.4 (48.4–54.6)	47.0 (44.9–49.1)	50.1 (46.4–53.8)[a]
HAD (Depression scale)	1.5 (0.6–2.4)	1.6 (0.7–2.5)	1.5 (0.8–2.5)
HAD (Anxiety scale)	3.2 (2.0–4.4)	2.5 (1.7–3.3)	3.1 (2.2–4.0)
DSST	74.3 (70.3–78.3)	74.6 (70.3–78.9)	74.6 (70.9–78.3)

Figures are expressed as means (95% confidence intervals).
[a]Pravastatin *vs* simvastatin difference significant $P = 0.05$.
No other Leeds Sleep Questionnaire variables showed significant differences.

mmol l^{-1}, (Significance of differences: simvastatin/placebo <0.0001, pravastatin/placebo 0.0018, simvastatin/pravastatin 0.021).

Although elevation of liver enzymes has been reported with HMG CoA reductase inhibitors, this effect was not found in the present study. Creatine kinase levels may be elevated in therapy with simvastatin and pravastatin but this effect did not occur in this study.

Haematological tests

No treatment effects on any of the haematological parameters measured were noted.

Correlations

No significant correlations between ratings on the Sleep Questionnaire and either plasma concentrations or EEG evoked potential magnitudes were demonstrated.

Adverse reactions

No subject reported severe adverse reaction and no-one withdrew from the study as a result of any side effect of the drugs.

Discussion

The results show that both simvastatin and pravastatin significantly lower plasma cholesterol levels in normal volunteers after 4 weeks of daily use. The effect was slightly greater with simvastatin than pravastatin, a finding consistent with clinical experience in patients with raised cholesterol concentrations [28]. That this effect was demonstrated supports the evidence from tablet counts that compliance was satisfactory.

The primary purpose of this study was to examine whether or not pravastatin or simvastatin caused measurable CNS effects and the complete absence of any significant effects on EEG evoked potentials provides strong evidence that neither drug exerts acute effects on brain activity. These EEG variables are extremely sensitive to the effects of centrally acting drugs and also to changes in attention and arousal [12–16]. Measurements were made at a time when blood concentrations of the drugs were expected to be maximal and effects on evoked potentials might be predicted to be most clearly demonstrated. Similarly, no drug effects were noted in the background EEG and particularly in the alpha (8–13 Hz) or beta (14–22 Hz) bands which are most sensitive to the effects of CNS stimulants or depressants [17].

In addition to the absence of any acute effects of the drugs on EEG measures, it can be inferred that there were no chronic (4 week) effects demonstrated on evoked potentials, anxiety or depression ratings or cognitive performance as measured by the DSST. Clearly the clinical significance of any association between low cholesterol and patient symptoms, e.g. depression depends to a degree on the strength of correlation between them. Low cholesterol levels have been associated with a higher risk of depression in elderly men [8] but there appeared to be no effect of lowering cholesterol on mood over a 4 week period in this study. In addition no significant correlations between cholesterol levels and any of the parameters measured was found. This might be explained by our subjects being younger and less susceptible to depression or because in this study cholesterol levels were lowered for a relatively short period. The subjects of Morgan and colleagues were not being treated for hypercholesterolaemia and therefore one would assume that their low cholesterol levels were fairly static. In case reports associations between simvastatin [29] and pravastatin [30] and depression have been suggested in hypercholesterolaemic patients. No association between these agents and depression was found in our study. This difference might again reflect the age of the subject or perhaps the chronicity of treatment (in general these case reports relate to treatment for greater than a month). However, one of the cases of Duits & Bos [29] developed psychotic depression after 4 days and another patient depressive illness after 1 month. The differences are not explicable in terms of the dose given as our subjects were given therapeutic doses of simvastatin and pravastatin. Furthermore cholesterol levels were lower in our subjects than in the case reports quoted. Controversy exists as to whether or not low cholesterol *per se* is associated with psychological morbidity and a recent study has implicated serum triglyceride rather than cholesterol as being linked to hostile acts and aggression [31].

An association between simvastatin and sleep difficulties has been described by Barth and colleagues [11]. In our study subjects indicated significantly greater difficulty in getting to sleep with simvastatin than pravastatin. However, there was no difference on a closely related question concerning time taken to get to sleep and neither drug differed from placebo. Furthermore the

effect was small and only reached significance at the 5% level. Given that 39 hypotheses were tested in the analysis of the sleep questionnaire it is possible that this result represents a type I error. Neither drug produced subjective changes in the frequency, vividness or unpleasantness of dreams and it would seem that simvastatin and pravastatin show minimal effects on sleep. This finding is in agreement with that of Black and colleagues [32]. No correlations were demonstrated between serum cholesterol concentrations, sleep ratings or EEG measures. Effects might be greater in an older clinical population (as sleep complaints increase in frequency with age [33]) than in our younger volunteer population. However our results are similar to those of Eckernas *et al.* [34] who found neither subjective nor objective (sleep EEG parameter) evidence of effects on sleep of pravastatin or simvastatin in an older clinical group. The present results do not suggest a relationship between sleep quality and blood cholesterol levels or HMG CoA reductase inhibitor therapy.

This study confirmed the hypothesis that pravastatin would not produce significant effects on brain activity. Similarly, simvastatin failed to show major CNS effects although it possibly increased difficulty getting to sleep. This investigation failed to show any effect on mood of either agent. Both simvastatin and pravastatin were well tolerated and caused no major side effects in our subjects and appear to be safe and effective in lowering cholesterol concentrations.

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