

SHORT PAPER

Caffeine levels following treatment of obstructive sleep apnoea

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Background: Randomised trials show that treatment of obstructive sleep apnoea (OSA) with nasal continuous positive airway pressure (CPAP) greatly improves sleepiness and also lowers diurnal systemic blood pressures (BP). Such patients consume more coffee than controls (presumably to combat their sleepiness) and might reduce their consumption following effective treatment, thus lowering BP by this mechanism rather than via a direct effect of alleviating OSA.

Methods: Plasma caffeine levels before and after treatment with either therapeutic (n=52) or subtherapeutic (control, n=49) CPAP were measured in stored blood samples from a previous randomised controlled trial of CPAP for 4 weeks in patients with OSA.

Results: There was a small significant rise in caffeine levels when the two groups were analysed as a whole (p=0.02), but not individually. Despite the fall in sleepiness measured objectively in the therapeutic CPAP group, there was no difference in absolute (or change in) caffeine levels between the two groups (mean (SE) $\mu\text{mol/l}$; therapeutic CPAP 9.2 (1.2), 10.2 (1.0), subtherapeutic 6.7 (0.9), 8.6 (0.9) before and after treatment, respectively).

Conclusion: Reduced coffee consumption is unlikely to be the explanation for the falls in BP following treatment of OSA.

Obstructive sleep apnoea (OSA) is known to cause excessive daytime sleepiness, and we have shown in randomised, placebo controlled, parallel trials (RCTs) that this symptom resolves following treatment with nasal continuous positive airway pressure (CPAP).^{1,2} Uncontrolled evidence also suggests that OSA causes diurnal systemic hypertension. In a similar later RCT we have also shown that nasal CPAP lowers both daytime and night time systemic blood pressures,³ as have others.⁴ However, recent evidence has also shown that patients with OSA drink, on average, nearly three times as much coffee as control subjects,⁵ presumably to combat their sleepiness. Caffeine is known to raise systemic blood pressure,⁶ and it has been suggested that the resolution of sleepiness following nasal CPAP might lead to reduced coffee consumption which might indirectly lower blood pressure rather than through the direct effect of abolishing sleep apnoea.⁷ We have therefore measured caffeine levels from stored plasma samples obtained during our first published randomised, placebo controlled trials of nasal CPAP in OSA.¹

METHODS

The full details of this RCT (performed and reported according to the CONSORT standards⁸) have been reported previously.¹ Briefly, 107 men with OSA (defined as >10/hour dips of >4% in arterial oxygen saturation overnight plus an Epworth Sleepiness Score (ESS) of ≥ 10) were randomised to receive either subtherapeutic nasal CPAP (which neither worsened nor improved their OSA) or fully therapeutic CPAP. Following arrival at the hospital at 08.30 hours, tests of sleepiness were performed before and after the treatment period of 4 weeks (modified maintenance of wakefulness test, MWT⁹). In addition, blood samples were taken on the study days at the same time (mid morning) and immediately spun and frozen at -60°C . Caffeine levels were analysed using an enzyme multiplied immunoassay technique (Syva Diagnostics, Dade Behring, Marburg, Germany). Forty nine patients completed 4 weeks of treatment with subtherapeutic CPAP and 52 completed treatment with therapeutic CPAP. No specific

instructions were given to the subjects about the consumption of caffeine containing substances, and there were no questionnaire data available on caffeine consumption.

Statistical analysis of caffeine levels was by *t* tests, paired or unpaired as appropriate, with conventional levels of significance (p<0.05).

RESULTS

Active nasal CPAP produced significant improvements in objectively measured sleepiness (median MWT rose from 22.5 to 32.9 minutes, p<0.0001); no such changes occurred in the control group receiving subtherapeutic CPAP.¹ Overall, the caffeine levels were similar to those found 4 hours after one cup of strong coffee (containing 150 mg caffeine) or 12 hours after two such cups.¹⁰ There were no significant differences between the absolute caffeine levels in the two groups, nor between the small changes in each group following treatment (therapeutic CPAP: mean (SE) caffeine level ($\mu\text{mol/l}$) 9.24 (1.15) before treatment, 10.22 (0.99) after treatment, difference +0.99 (0.72); subtherapeutic CPAP (control): 6.73 (0.86) before treatment, 8.57 (0.94) after treatment, difference +1.84 (0.93)). The actual non-significant difference between the changes in caffeine levels found in the two groups was 0.84 $\mu\text{mol/l}$ (95% CI -1.47 to +3.18). Interestingly, in the two groups analysed together there was a small but statistically significant increase in caffeine levels (+1.4 $\mu\text{mol/l}$, 95% CI +0.25 to +2.56, p=0.017), but not in either group analysed individually. There were no significant correlations between caffeine levels and either measure of sleepiness (ESS or MWT) at either time point, although there was a strong correlation between the caffeine levels measured on the two occasions (0.67, p<0.0001).

DISCUSSION

No significant difference in caffeine consumption was seen between the two groups following the trial period and, indeed, there was a small increase in caffeine levels in both groups. It therefore seems unlikely that reductions in caffeine levels are

the explanation for the fall in 24 hour blood pressures seen only in the group receiving therapeutic nasal CPAP.³ A limitation of the study is that the samples were analysed approximately 4 years after the original study. However, the samples were stored all together in plastic tubes in a freezer at -60°C and analysed in one batch. Caffeine is thought to be stable under these conditions and any decay should have affected all samples equally, thus producing no systematic bias that could invalidate the conclusions of the study. In this dataset from our original study¹ only casual blood pressures were available on all 101 subjects and 24 hour data in 39. A greater fall in blood pressure in the therapeutic group than in the subtherapeutic group was subsequently found to be statistically significant in a larger group of patients where the number of 24 hour blood pressure results available was 118.³ However, the magnitude of the blood pressure changes between the therapeutic and subtherapeutic groups, on which this current paper is based, were of similar magnitudes to the later trial but did not reach statistical significance.

In conclusion, it seems unlikely that reductions in caffeine levels are a significant confounding variable influencing measurements of blood pressure following treatment of OSA for 4 weeks with nasal CPAP and resolution of sleepiness.

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G Robinson and J Pepperell were involved in performing the study, J Stradling and R Davies initiated the study, and J Stradling wrote the report.

Conflict of interest: none.

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LUNG ALERT

Exposure to nitrogen dioxide may be associated with severity of virus related asthma exacerbations

▲ Chauhan AJ, Inskip HM, Linaker CH, *et al*. Personal exposure to nitrogen dioxide (NO₂) and the severity of virus-induced asthma in children. *Lancet* 2003;**361**:1939–44

Respiratory viruses are considered to be one of the main triggers of asthma exacerbations in children. Exposure to nitrogen dioxide (NO₂), a common environmental pollutant, has been linked to respiratory symptoms in both children and adults. Whether high individual exposure to NO₂ increases the severity of asthma exacerbations caused by common viruses remains unclear.

This prospective study looked at 114 asthmatic children, all living in non-smoking homes, between the ages of 8 and 11 years. Participants recorded upper and lower respiratory tract symptoms and peak flow measurements for up to 13 months. In addition, weekly personal NO₂ exposure was measured with the aid of diffusion tubes kept on clothing during the day. At the onset of a respiratory tract illness nasal aspirates were taken which were subsequently screened for common viruses plus atypical bacteria. For all viruses together and respiratory syncytial virus alone, significant increases in respiratory tract symptoms were associated with a greater exposure to NO₂ in the week before infection. In terms of reduction in peak flow, there was an association with greater NO₂ exposure in the week before infection with picornavirus alone.

This study concluded that high personal exposure to NO₂ may be associated with an increase in the severity of virus induced asthma exacerbations. These findings should make the medical, scientific, and political communities aware of potential health and financial benefits when air pollution measures are employed.

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