Effect of caffeine on histamine bronchoprovocation in asthma

Antoinette Colacone, Luisa Bertolo, Norman Wolkove, Carol Cohen, Harvey Kreisman

Abstract

It was recently reported that caffeine may reduce the clinical symptoms of asthma and may prevent the clinical manifestations of this disease. The effect of caffeine on histamine responsiveness is unknown. The effect of caffeine (5 mg/kg) and placebo on histamine responsiveness (the provocation concentration causing a 20% fall in FEV₁, PC₂₀) was studied in 10 subjects with mild asthma (prechallenge FEV₁ 84% of predicted value). The PC₂₀ for histamine bronchoprovocation after caffeine ingestion was 2.65 (95% confidence limits 0.99, 7.10) mg/ml. After placebo the PC₂₀ was 1.89 (0.96, 3.71) mg/ml. It is concluded that caffeine in a dose equivalent to about three cups of coffee has a very small effect, if any, on histamine bronchoprovocation in those with mild asthma. Specific instructions about not having drinks containing caffeine before histamine challenge are therefore not necessary.

An inverse correlation between coffee intake and the prevalence of asthma was reported recently.¹ The risk of asthma was 20% less in those who consumed two or more cups a day than in those who drank none. The bronchodilator effect of caffeine may reduce the clinical symptoms of asthma or prevent the clinical manifestations of the disease.¹ Asthma may be underdiagnosed therefore in a coffee consuming population.

Current guidelines for the laboratory diag-

nosis of asthma sometimes include testing for bronchial hyperreactivity to specific or non-specific stimuli. Histamine bronchoprovocation challenge is often used to measure non-specific airway reactivity in the laboratory or in population surveys.² Anti-asthmatic medication, including theophylline, may attenuate the bronchoconstriction induced by histamine and specific recommendations exist for withholding these medications before bronchoprovocation testing.^{3,4} There are no specific guidelines, however, for caffeine intake before testing.

The purpose of this investigation was to study whether caffeine at a dose of 5 mg/kg (about 3 cups of coffee) would alter histamine reactivity in adults with mild bronchial asthma. We chose this dose because the average caffeine content in a cup of coffee is about 150 mg and only 19% of the population have more than three cups a day.^{1,8}

Methods

SUBJECTS

We studied 10 symptom free asthmatic subjects (seven male) with a mean age of 46 (SD 17) years. Nine subjects had previously documented increased airway reactivity (a provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) less than 8 mg/ml), and the other had a history of seasonal asthma and a PC₂₀ of less than 16 mg/ml. Before the study seven subjects used an inhaled beta agonist, five theophylline and four an inhaled corticosteroid; two required no medication. The four patients taking inhaled steroids (Nos 2, 5, 7, 8 in the table)

**Pulmonary Division,
Department of
Medicine, Sir
Mortimer B Davis-
Jewish General
Hospital, Mount Sinai
Hospital and McGill
University, Montreal,
Quebec, Canada**
A Colacone
L Bertolo
N Wolkove
C Cohen
H Kreisman

Address for reprint requests:
Dr Harvey Kreisman, c/o
Pulmonary Division, Sir
Mortimer B Davis-Jewish
General Hospital, 3755 Cote
St Catherine Road,
Montreal, Quebec, Canada
H3T 1E2.

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Individual caffeine doses, serum concentrations, and their effect on bronchial responsiveness to histamine (PC₂₀)

Patient No	Weight (kg)	Caffeine dose (mg)	Serum caffeine concentration (µg/ml)	PC ₂₀ (mg/ml)		%ΔFEV ₁ slope (mg/ml)	
				Placebo	Caffeine	Placebo	Caffeine
1	73	365	2.5	0.6	4	1.7	3.0
2	95.5	477	4.5	1.4	0.4	3.6	3.0
3	110	550	6.7	2.3	16	17.8	47.2
4	70	350	5.4	6	11	10.2	0.5
5	84.5	425	6.0	0.6	0.6	3.6	1.8
6	57.5	289	6.5	2.5	2.2	38.6	41.4
7	107	535	5.7	1.5	1.5	8.7	14.3
8	65	325	5.7	6	8.8	2.6	2.2
9	71	355	6.3	0.7	0.6	11.0	9.1
10	76	380	4.7	5.8	6.8	12.2	16.5
Mean	81	405.1	5.4	1.9*†	2.7*†	7.4*†	6.1*†
SD	17.8	88.9	1.2	(1.0, 3.7)	(1.0, 7.1)	(2.1, 17.5)	(3.7, 14.7)

*Geometric means with 95% confidence intervals in parentheses.

†p = 0.31 in the comparison of PC₂₀ after placebo and after caffeine.

‡p = 0.61 in the comparison of slope after placebo and after caffeine.

Figure 1 Identity plot showing prechallenge FEV_1 (l) of individual subjects on the two study days. Mean (SD) FEV_1 caffeine 2.65 (0.73) l, placebo 2.67 (0.78) l.

took the same doses before and during the study.

The protocol was approved by the ethics committee of the Sir Mortimer B Davis-Jewish General Hospital. Informed consent was obtained from each subject.

TEST MEDICATIONS

Caffeine and corresponding placebo were prepared in solution and coded by the hospital pharmacy. The former contained caffeine citrate in a concentration of 50 mg/ml. Both solutions contained amaranta colorant and vanilla essence diluted with distilled water and were indistinguishable by taste, colour, and smell.

STUDY PROTOCOL

The subjects were randomised to receive caffeine and placebo first in a double blind crossover study. The study was carried out at

the same time of day on two days within two weeks.

Before each study subjects were asked to refrain from consuming products containing caffeine for 48 hours and to fast for eight hours. Antiasthmatic medications were withheld according to standard guidelines for histamine bronchoprovocation testing.⁴ Beta agonists and anticholinergic drugs were withheld for 8–12 hours and theophylline for 24 hours before testing. Slow release theophylline and antihistamines were not consumed for 48 hours before testing. Steroids were continued as usual.

Spirometry was performed with a recording spirometer (Vitalograph, Model S, Kansas City, Missouri). Baseline spirometric tests were carried out in triplicate and the FEV_1 was recorded from the best spirogram (sum of FEV_1 and forced vital capacity). Subjects then ingested either caffeine (5 mg/kg body weight) in aqueous solution or an equivalent volume of placebo.

Blood for serum caffeine and theophylline determination was drawn 105 minutes after ingestion of the test medication. The blood samples were then centrifuged and stored at -20°C . Caffeine and theophylline concentrations were later determined by high pressure liquid chromatography.⁵

Spirometry was repeated two hours after ingestion and followed by a histamine challenge test performed according to the method of Cockcroft *et al.*⁶ A Wright nebuliser was filled with 3 ml of solution and operated at a flow of 9 l/min 50 lb/in². The nebuliser output had been calibrated to deliver a mean of 0.26 (SD 0.008) ml over two minutes. Increasing doses of histamine were given until a 20% fall in FEV_1 had occurred.

STATISTICAL ANALYSIS

Arithmetic means and standard deviations were computed for FEV_1 . PC_{20} values were log transformed before analysis; geometric mean values and 95% confidence intervals are given. The slope of the histamine dose-response curve was calculated by linear regression and log transformed before analysis by paired *t* test. Student's paired *t* test was used to compare differences between placebo and caffeine data. A *p* value below 0.05 was considered statistically significant.

Results

Mean (SD) FEV_1 values before histamine challenge did not differ significantly on the caffeine and placebo days (2.65 (0.73) and 2.67 (0.78) litres; fig 1); both values were 84% of the predicted FEV_1 .⁷ Mean (SD) FEV_1 increased by 0.10 (0.09) l after caffeine compared with 0.05 (0.06) after placebo (*p* = 0.38). The mean (SD) serum caffeine concentration was 5.4 (1.23) $\mu\text{g/ml}$ after caffeine; none was detected after placebo (table). Theophylline was not detected in the serum of any patient on either study day.

All subjects had a PC_{20} of 16 mg/ml or less after both caffeine and placebo. There was no

Figure 2 Bronchial responsiveness to histamine (PC_{20} , mg/ml) on caffeine and placebo days. Two subjects had a two concentration increase in PC_{20} and another had a similar reduction in PC_{20} on the placebo day.

significant difference in PC_{20} values or in the slope of the dose-response relationship between caffeine and placebo (table and fig 1). The PC_{20} increased by more than two dose concentrations in two subjects after caffeine and decreased by two dose concentrations in one (fig 1). There was no relation between serum caffeine concentrations and change in PC_{20} (table). The two subjects showing the greatest increase in PC_{20} had the highest (6.66 $\mu\text{g/ml}$) and lowest (2.50 $\mu\text{g/ml}$) caffeine concentrations (table).

Discussion

We have shown that caffeine, in a dose that produced a mean serum caffeine concentration of 5.4 $\mu\text{g/ml}$, did not substantially alter airway reactivity in a group of symptom free asthmatic subjects and caused no significant bronchodilatation. The effect of dietary consumption of caffeine on histamine responsiveness has not been examined previously. A recent epidemiological study suggested that caffeine may suppress symptoms to such a degree that the clinical diagnosis of asthma is prevented.¹ We wondered whether caffeine might also alter the result of bronchoprovocation testing. Our results suggest that caffeine is not likely to have a large effect on the response to histamine challenge and prior intake of moderate amounts of caffeine is unlikely to be important in epidemiological or clinical studies using bronchoprovocation.

It is not surprising that caffeine does not protect against histamine or carbachol bronchoprovocation whereas theophylline may have this effect. Caffeine is only 40% as active as an equivalent molar dose of theophylline.⁸ Moreover, the protective effect of theophylline has not been consistent.^{3,9} In studies where an effect has been seen the protection was dose dependent and was greatest in subjects with the lowest PC_{20} .^{3,10,11} It is therefore possible that higher doses of caffeine given to more reactive asthmatic patients might afford some protection. The dose of caffeine would be greater however than that usually consumed by most individuals.¹⁸

Our subjects did not bronchodilate in response to caffeine whereas most but not all other studies have demonstrated some bronchodilatation.^{8,12,13,14} The studies that showed bronchodilatation tested individuals with more severe asthma or gave larger doses of caffeine than we did. This response may be related to increased concentrations of plasma adrenaline, an increase of 257% (SD 58%) in one study after ingestion of caffeine producing a plasma concentration of 5.9 (0.5) $\mu\text{g/ml}$.¹⁵ Ingestion of a higher dose of caffeine may have produced bronchodilatation but such a dose would be irrelevant to usual coffee consumption. Our subjects had normal or nearly normal pulmonary function and therefore had little room for improvement after caffeine ingestion.

The serum caffeine concentrations in this

study were lower than expected from a dose of 5 mg/kg caffeine.^{8,14} A given dose of caffeine, like theophylline, may produce a wide range of serum concentrations in different individuals. For instance, Crivelli *et al* found that after a weight adjusted dose of caffeine individual serum concentrations differed by as much as twofold.¹² The mean peak concentration they achieved 60 minutes after ingestion of 6 mg/kg of caffeine (7.6 (SD 2.1) $\mu\text{g/ml}$) is consistent with the 5.4 (1.23) $\mu\text{g/ml}$ achieved in our study 105 minutes after a dose of 5 mg/kg.

Possibly a "time" error accounts for the lack of difference noted in this study. Peak caffeine concentrations are seen 45–60 minutes after ingestion^{8,12,13} and the serum concentration does not fall for at least another 30 minutes.¹² Bronchodilatation when it occurs is maximal 120 minutes after ingestion.^{8,13} As we measured PC_{20} at 120 minutes we are unlikely to have missed the peak effect of caffeine on PC_{20} .

In conclusion, caffeine in dietary concentrations is unlikely to have an effect on the results of histamine bronchoprovocation in those with mild asthma. Specific instructions on caffeine intake are not necessary before bronchoprovocation testing.

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