Effect of temazepam on tracheobronchial mucus clearance

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Abstract

Background Tracheobronchial clearance of mucus from the lungs is reduced during sleep and, usually, by the administration of opiates. It seemed possible therefore that temazepam, a widely used potent benzodiazepine, retarded clearance.

Methods The effect of 10 mg temazepam on mucociliary clearance was studied in eight healthy volunteers, aged 18-50 (mean 30) years, in a randomised, placebo controlled, double blind, cross-over study. Six subjects were female and two male. Six were non-smokers and two were light current smokers. Clearance was assessed from the change in radioactivity in the lungs after inhalation of 5 µm diameter polystyrene particles, labelled with technetium-99m, under controlled conditions.

Results Tracheobronchial clearance was reduced by 22% after temazepam by comparison with placebo during the first three hours after drug ingestion; this is the period when circulating drug concentrations are highest.

Conclusion Temazepam should be prescribed with caution in patients with impaired lung mucociliary transport.

Temazepam, a benzodiazepine, is extensively prescribed in general and hospital practice to induce sleep.¹ It also possesses powerful anxiolytic, muscle relaxant, and anticonvulsant activity.

Mucociliary clearance² is a non-specific host defence clearance mechanism, which together with cough³ helps to keep the lungs clean and sterile even when exposed to a polluted environment. Clearance may be adversely affected by several factors,⁴ including lung diseases, such as chronic bronchitis and asthma, and pharmacological agents, such as β blocking and anticholinergic drugs.

With a few exceptions,⁵ opiates appear to depress mucociliary clearance⁶ and they inhibit mucus secretion in human bronchi.⁷ Narcotics reduce ciliary activity of the oyster gill.⁸ Codeine and normethadone depress ciliary beat frequency in a dose dependent fashion in animals,⁹ and subcutaneous codeine and morphine slow tracheobronchial clearance in the cat for several hours.¹⁰

Lung mucociliary clearance and cough are reduced in normal subjects and asthmatic

patients during sleep.¹¹ The effect of benzodiazepine on lung mucociliary clearance in man has not been described previously.

We report the effect of a single dose of temazepam on lung mucociliary clearance in healthy volunteers.

Methods

SUBJECTS

Eight healthy volunteers (six female, two male) participated in the study. Their mean (SE) age, height, and weight were 30 (4) years, 1.64 (0.03) m, and 65 (4) kg. Six subjects were non-smokers and two (both women) were current smokers with a tobacco consumption of six and eight pack years.

METHODS

A double blind, randomised, placebo controlled, crossover, within subject study was carried out. The volunteers attended the laboratories on two separate study days at least one week apart. On arrival in the laboratory their forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and maximum mid expiratory flow (MMF₂₅₋₇₅) were measured with a dry bellows spirometer (Vitalograph) and their peak expiratory flow (PEF) with a Wright's peak flow meter. For each pulmonary function index the highest value of three technically acceptable measurements was recorded.

Tracheobronchial clearance was measured by an objective, non-invasive radioaerosol technique.¹² Under strictly controlled conditions, subjects inhaled 5 µm monodisperse polystyrene particles labelled firmly with the gamma emitting radionuclide technetium-99m (^{99m}Tc; half life six hours). The radioaerosol was inhaled in discrete breaths of 450 ml each from around functional residual capacity. Each breath was followed by a three second breath holding pause to allow particles to be deposited by gravity.¹³ Inspiratory flow was measured by a pneumotachograph and recorded on an ultraviolet recorder. After the inhalation of radioaerosol subjects were asked to rinse their mouth with water to clear the oropharyngeal region of radioaerosol and they subsequently swallowed some water to rinse the oesophagus. Immediately after inhalation the subjects were seated between two suitably collimated scintillation counters located anteroposteriorly to the chest. The field of view of these detectors included most of both lungs but excluded radioactivity from the stomach.¹⁴ Counts were taken at half hour intervals for the next six

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hours with a final count of lung radioactivity at 24 hours.

The radioactivity remaining in the lungs at 24 hours was taken to represent "alveolar deposition"—that is, radioaerosol deposited beyond the reach of mucociliary clearance.¹⁵ The activity representing alveolar deposition was subtracted from the whole lung count. The tracheobronchial data were expressed as a percentage of the initial count. Tracheobronchial clearance was assessed by measuring the area under the curve (AUC), with the trapezoidal rule, for the first three hours and for the whole six hours of observation.¹⁶ The area under the curve represents tracheobronchial retention. The larger the AUC the greater is the tracheobronchial retention and the slower the clearance.

Within 10 minutes of the first count the subjects sat in front of a large field of view gamma camera (Ohio-Nuclear 110) linked to a computer (Nodecrest V77-600) and the initial topographical distribution of the radioaerosol within the lungs was expressed quantitatively as a penetration index.¹⁷ This is defined as the ratio of radioactivity in the outer region of the lungs to that in the inner region divided by the ratio of radioactive krypton-81m (half life 13 seconds) in the two regions.

Fifteen minutes before inhaling the radioaerosol subjects were asked to swallow 5 ml of an elixir (glycerol based) containing 10 mg of temazepam or placebo (the vehicle minus the active drug), which was indistinguishable in taste and appearance from the active preparation.

STATISTICAL ANALYSIS

As the data were not normally distributed the Wilcoxon test for paired differences was used in the statistical analysis with the Spearman rank correlation test.¹⁸ The level of significance was taken as $p < 0.05$.

Results

Five subjects received placebo treatment first and three temazepam. Pulmonary function

Table 1 Mean (SE) baseline pulmonary function indices (expressed as percentages of predicted values) for the eight healthy volunteers on the placebo and temazepam study days

	Placebo	Temazepam	p
FEV ₁	115 (5)	113 (5)	NS
FVC	116 (5)	114 (5)	NS
PEF	115 (8)	116 (7)	NS
MMF ₂₅₋₇₅	95 (11)	91 (10)	NS

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; PEF—peak expiratory flow; MMF₂₅₋₇₅—maximum mid expiratory flow.

Table 2 Mean (SE) radioaerosol inspiratory flow rate, alveolar deposition, and penetration index for the eight healthy volunteers on the placebo and temazepam study days

	Placebo	Temazepam	p
Flow rate (l/min)	44 (3)	37 (3)	<0.01
Alveolar deposition (%)	49 (3)	52 (5)	NS
Penetration index	0.65 (0.05)	0.70 (0.05)	NS

Mean (SE) tracheobronchial retention curves for eight healthy volunteer subjects after placebo and temazepam treatment.

indices were no different after temazepam and after placebo (table 1). The mean (SE) radioaerosol inspiratory flow rate, alveolar deposition, and penetration index for the study group for the placebo and temazepam study days are shown in table 2. The radioaerosol was inspired at a significantly higher flow rate on the placebo day than on the temazepam day ($p < 0.01$). There were no significant differences between the two study days for alveolar deposition or penetration index. Three subjects recorded dry, unproductive coughs or throat clearing, or both, during the six hour observation periods on both the placebo and the temazepam days. The frequency of coughing was similar within subjects on the two study days.

Tracheobronchial clearance was significantly slower over the first three hours after treatment with temazepam than with placebo (mean (SE) AUC₀₋₃ 132% (11%)/h for placebo and 161% (10%)/h for temazepam; $p < 0.05$). Although the AUC₀₋₆ for the six hour observation period (figure) was greater (that is, clearance was slower) after temazepam (200% (16%)/h) than after placebo (166% (15%)/h) the difference was not significant ($p < 0.10$). The correlation coefficient (r_s) for the relation between the dose of drug/unit body weight and percentage change in AUC₀₋₃ was 0.63 ($p < 0.10$). (The value of r_s required for $p < 0.05$ is 0.64.)

Discussion

Tracheobronchial clearance of deposited radioaerosol depends on the initial distribution of the radioaerosol within the lung. This distribution is a function of the physical properties of the aerosol, the mode of inhalation, and the patency of the airways.¹⁹ The radioaerosol was inspired at a higher flow rate with placebo than with temazepam, but the difference was small and alveolar depositions and penetration indices during the two study days were similar (table 2). Thus the proportions of radioaerosol available for clearance by mucus transport after placebo and temazepam administration were similar.

The AUC was used as an index of tracheobronchial clearance as it reflects clearance over an observation period and avoids multiple statistical testing at numerous time points.

Lung mucociliary clearance was less (mean percentage increase in AUC 25%) during the first three hours after temazepam administration than after placebo. Although a similar reduction in the area under the curve was seen over the six hours of observation it failed to attain statistical significance.

A study on the pharmacokinetics of temazepam elixir in healthy male volunteers showed a mean time to peak plasma concentration of 1.6 hours.²⁰ The mean drug distribution and terminal phase half lives were about 1.3 and 9 hours respectively.

The tracheobronchial retention curves diverged over the first two hours after radioaerosol administration, with convergence of the curves thereafter. The maximum separation between the tracheobronchial retention curves occurred at about 1.5 hours, and this coincides with the peak plasma concentrations. Tracheobronchial clearance had returned to normal some five hours after the administration of temazepam, which is before the washout time of the drug is completed (terminal phase $T_{1/2} = 9$ hours). Neither the half life nor clearance of temazepam is significantly related to age.²¹ Although clearance of total temazepam is higher in men than in women²¹ (on the assumption of complete absorption) this is not relevant to our study, in which six of the eight subjects were women.

The reduction in tracheobronchial clearance after temazepam treatment could have arisen because of altered cough, reduced diaphragm movement, or altered ciliary function. Tracheobronchial clearance comprises mucociliary clearance and cough. The frequency of coughing in the three subjects who did cough was similar on the two study days and was low in two of the three subjects; tracheobronchial clearance must therefore reflect mucociliary clearance in this study.

It has been reported recently that tracheobronchial clearance of patients with bilateral diaphragmatic muscle weakness is less than in healthy control subjects.²² Reduced mechanical movement of the lungs after temazepam as a result of a reduced respiratory rate is a possible explanation for the reduction in mucus clearance in our study, though respiratory rate was not measured.

Efficient mucociliary transport depends on the intricate interrelationship between several components of this host defence mechanism, including the integrity of the ciliated epithelium, the thickness and consistency of the periciliary layer, ciliary beat frequency and coordination of the ciliary beat, and the quantity and consistency of the secretions overlying the cilia. Opiates have been reported to reduce ciliary beat frequency¹⁰ and mucus secretion,⁷ both of which are essential for proper clearance. There is no evidence, however, that temazepam has the same effect.

Tracheobronchial clearance is less in the elderly^{23,24} than in younger subjects and in patients with respiratory disease, such as chronic bronchitis,²⁵ asthma,²⁶ and bronchiectasis.²⁷ Sleep will also reduce tracheobronchial clearance in both healthy and asthmatic subjects. A reduction in tracheobronchial clearance must result in retention of lung

secretions and may increase the incidence of chest infections²⁸ in patients in high risk groups.²⁵⁻²⁷

The administration of temazepam at night in patients with chronic bronchitis, asthma, and bronchiectasis may have an important adverse effect on lung function.

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