EFFECT OF A MIXTURE OF PYRIDOSTIGMINE AND ATROPINE ON FORCED EXPIRATORY VOLUME (FEV₁), AND SERUM CHOLINESTERASE ACTIVITY IN NORMAL SUBJECTS

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Inhibition of acetylcholinesterase (A-ChE) activity by cholinesterase (ChE) inhibitors is used clinically to reverse the effects of non-depolarizing neuromuscular blocking drugs. Certain muscarinic side-effects such as bradycardia are antagonized by atropine administered either simultaneously (Baraka et al., 1981) or before the ChE inhibitor (Katz, 1967). However, when these reversal agents are administered at the end of surgery, just before extubation of the trachea, bronchial constriction and increases in bronchial secretions are muscarinic side-effects of particular importance. At this time other drugs which can influence bronchomotor tone will have been given, and it will be difficult to distinguish between the specific actions of the individual drugs. The present study was designed to investigate whether the muscarinic side-effects in the lung are fully antagonized when a combination of pyridostigmine and atropine is administered i.v. in clinical doses to normal subjects receiving no other medication before or during the study.

SUBJECTS AND METHODS

The study was performed in six healthy male volunteers (28-34 yr) with no previous history of asthma. All gave informed consent. The procedure was approved by the Regional Ethics Committee.

Each subject received pyridostigmine 0.143 mg kg⁻¹ (maximum 10 mg) mixed with atropine 0.0143 mg kg⁻¹ (maximum 1 mg) i.v. over 1 min. Forced expiratory volume in the first 1 s (FEV₁) was used to evaluate bronchial constriction.

Serum cholinesterase (S-ChE) activity (E.C.3.1.1.8) was measured in blood samples drawn at specified time intervals from the antecubital vein of the arm opposite to that used for administration of the anti-ChE drug. The method of Kalow and Genest (1957) was used to determine S-ChE activity. The dibucaine number was measured for characterization of the phenotype of S-ChE (Kalow and Genest, 1957). The normal range in our laboratory for S-ChE activity (n = 453) was: 680–1560 u. litre⁻¹ (Viby-Mogensen and Hanel, 1977), with a coefficient of variation.
of 0.015–0.020. All persons tested had normal S-ChE activity and a normal dibucaine number.

During the study the ECG and arterial pressure were monitored continuously. Statistical evaluation was performed using a polynomial regression analysis.

RESULTS

The changes in S-ChE activity with time are shown in figure 1. The S-ChE activity before injection of pyridostigmine was within normal limits. The maximum depression of S-ChE activity occurred 5 min after injection, the activity decreasing to 27 ± 5% (mean ± SEM) of the initial value. Serum ChE activity returned to 50% of its initial activity after 18 ± 4 min (table I). The mean changes in FEV₁ with time after treatment calculated as percent of initial value are presented in figure 2. During the first part of the test period, which coincided with the maximal depression of S-ChE activity, no significant change in FEV₁ was observed. At the end of the observation period a small but significant (P < 0.05) increase in FEV₁ was registered.

The heart rate increased within 2 min in all subjects from the initial measurement of 77 ± 4.2 beat min⁻¹ to a maximum mean of 101 ± 10.4 beat min⁻¹.

During the first 25 min after injection, all of the subjects felt some minor discomfort, characterized by generalized muscle twitches, dysfunction of the tongue and swallowing reflex, and paralysis of accommodation of varying degrees. These symptoms disappeared totally before the end of the test period.

DISCUSSION

The clinical use of ChE inhibitors may be limited because of undesirable muscarinic side-effects. It is known that the muscarinic side-effects on the heart can be prevented by the simultaneous administration of atropine (Kemp and Morton, 1962; Baraka, 1968; Kjellberg and Tammisto, 1970; and Rosner, Kepes and Foldes, 1971). However, the muscarinic side-effects on oropharyngeal secretions and bowel peristalsis are not totally abolished when the anticholinesterase–atropine mixture is used, and this may be important following gastrointestinal surgery (Hannington-Kiff, 1969). Similarly, if anticholinergic muscarinic side-effects causing bronchoconstriction were to persist despite the use of atropine, this would be of significance in patients with pre-existing lung disease. No previous reports have examined bronchial function in patients treated with an anticholinesterase–atropine combination such as is used in clinical practice.

In the present study, S-ChE activity was measured. The ultimate measure of motor endplate ChE can be obtained only from muscle biopsies and is
therefore rarely, if ever, measured clinically. S-ChE activity was measured to enable us to compare our results with those from previous reports using different ChE inhibitors. It is known that ChE inhibitors will effect their pharmacological activity in any tissue containing ChE and that there is a parallelism between the therapeutic efficacy and the inhibitory effect of pyridostigmine on circulating ChE (Grob, Garlick and Harvey, 1950; Foldes and Smith, 1966). Furthermore, pyridostigmine is a more potent inhibitor of motor endplate ChE activity than of S-ChE. Therefore, our measures of S-ChE activity represent an underestimation of the changes in muscle endplate A-ChE—the pharmacologically active agent in neurotransmission (Namba et al., 1980).

Pyridostigmine was used in a dose of 0.143 mg kg⁻¹. This was found to depress S-ChE activity by 73 ± 7%, and is comparable to the results reported by Baraka and colleagues (1981). They found that S-ChE activity was depressed by 70 ± 2% by pyridostigmine 0.25 mg kg⁻¹; neostigmine 0.05 mg kg⁻¹ depressed S-ChE activity by 63 ± 7% (pyridostigmine 10 mg is equipotent to neostigmine 2.5 mg as an antagonist of tubocurarine). Serum-ChE in subject number 1 was only reduced to 67% of the initial value. However, the subjective minor discomforts, and the initial increase in heart rate in this individual were similar to those observed in the other subjects. The discrepancy must reflect physiological differences in sensitivity to the drug.

FEV₁ measurements are widely used to evaluate the effect on airway resistance of other pharmacological agents. It is an accepted determinant of bronchial obstruction following bronchial challenge (Cropp et al., 1980). The initial fluctuations in FEV₁ were not significant from a clinical or a statistical point of view. Furthermore, the maximal reduction in FEV₁, of −1.6% of initial values, occurred 9 min after maximal depression of S-ChE was observed. Although no significant decrease in FEV₁ was observed, there was a small but significant increase by the end of the study period. These findings indicate that pre-existing vagal tone is not increased, but rather decreased by the simultaneous administration of the pyridostigmine–atropine mixture.

Atropine, therefore, appears to be an effective antagonist of the possible muscarinic bronchoconstrictor effects of pyridostigmine in non-asthmatic individuals. In asthmatic patients the bronchi may have a lower threshold for vagal stimulation (Gold, 1975; Miller, Fish and Patterson, 1977), but atropine has been demonstrated to protect these patients from allergen-induced bronchospasm (Yu, Galant and Gold, 1972). Whether atropine can also effectively antagonize the possible muscarinic bronchoconstrictor effects of pyridostigmine in asthmatics remains to be documented.

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REFERENCES
