Effect of glycopyrrolate and atropine on thermoregulation after exercise

K. H. SIMPSON, J. H. GREEN & F. R. ELLIS

University Department of Anaesthesia, Clinical Sciences Building, St James's University Hospital, Leeds LS9 7TF

1 The effects of two anticholinergic drugs on heat production (derived from oxygen consumption), sweating and core and skin temperature were compared with saline placebo in five healthy volunteers, before and after exercise.

2 There were no significant differences between the groups in resting and peak heat production after exercise. Sweat evaporation rate increased after exercise in all cases, but there was individual variation in response to the drugs. Sweat evaporation was greater after saline placebo compared with atropine, but not after glycopyrrolate compared with saline placebo or atropine.

3 In the saline placebo group, increased sweat evaporation following exercise was reflected by an initial fall, in skin temperature. Following anticholinergic drugs, skin temperature increased after exercise without an initial decrease. Core temperature increased following exercise, but there were no significant differences between the anticholinergic drugs and saline placebo.

4 Although clinical doses of anticholinergic drugs, when compared with saline placebo, inhibited sweating after exercise, core temperature was not significantly increased. Therefore it is suggested that non-evaporative heat loss compensated for the reduction in sweating due to anticholinergic drugs.

Keywords anticholinergic drugs heat stress sweating

Introduction

Anticholinergic drugs in large doses cause an increase in core temperature, which is mainly due to inadequate heat loss associated with a reduction in sweating. It has also been suggested that high doses of atropine may lead to increased heat production via central mechanisms (Stoll, 1948). Mirakhor & Dundee (1980) observed that atropine and glycopyrrolate in clinical doses led to an increase in oral temperature in resting subjects, with a maximum rise of 0.3° C. Elevation of core temperature with anticholinergic drugs is exacerbated by pre-existing pyrexia or exercise. After strenuous exercise by men acclimatized to a warm environment, 2 mg of intramuscular atropine further elevated rectal tem-

perature by 0.6–0.9° C (Cullumbine & Miles, 1955).

During thermal equilibrium metabolic heat production is equal to heat loss, classically described as:

$$\text{Heat production} = \text{Evaporation} \pm \text{Convection} \\ \pm \text{Conduction} \pm \text{Radiation} \pm \text{Heat storage}.$$

The rationale for carrying out the present study was to investigate the effects of glycopyrrolate and atropine on variables involved in this formula.

Equipotent doses of the anticholinergic drugs for inhibition of sweating were chosen (Mirakhor & Dundee, 1980), and sweat evaporation rate was measured. In this way any change in core

temperature may be explained by differences in heat production or variables involved in heat loss, other than sweating. This work has been presented to the Anaesthetic Research Society (Ayling *et al.*, 1986).

Methods

Subjects and study design

Five healthy male volunteers, aged 23–30 years, gave written informed consent to take part in the study, which was approved by the Hospital Ethics Committee. Subjects were within 10% of their optimum weight, had no respiratory or cardiac disease and were not taking drugs, although one subject was a smoker. Each subject acted as his own control and performed three experiments which took place on different days, at least one week apart. The studies were carried out in an ambient dry bulb temperature of $25.5 \pm 0.3^\circ\text{C}$ (mean $\pm$ s.e. mean), the maximum temperature change during any experiment was a gradual rise of 1.6°C . Relative humidity was $47.6 \pm 1.2\%$ (mean $\pm$ s.e. mean). The exercise test used in this study is very strenuous, and it was deemed important to ensure that the subjects were able to tolerate the work under drug-free conditions, therefore on the first occasion subjects received saline placebo (S). On the other two occasions either atropine (A) or glycopyrrolate (G) was given. A nominated anaesthetist was responsible for the subjects' clinical condition, and for safety the electrocardiograph was monitored throughout.

Each experiment commenced at 09.30 h to reduce the effect of diurnal variation of thermoregulation. Subjects ate a light breakfast, but refrained from caffeine and smoking during the preceding 8 h. During each experiment they wore shorts and lay on a couch.

Repeated measurements were made of insulated external auditory meatal temperature, skin temperature, sweat evaporation rate and respiratory gas exchange. Each experiment comprised a 30 min control period, after which saline placebo, 0.015 mg kg^{-1} atropine or 0.003 mg kg^{-1} glycopyrrolate was given intravenously. Measurements continued for 30 min following injection and then the subjects carried out a standardised 5 min, 19 inch Harvard Step Test (Åstrand & Rodahl, 1977). They rested for 1 h after exercise whilst the measurements were continued.

Measurement of temperature

External auditory meatal temperature was measured every 5 min using a thermistor em-

bedded in a plastic earmould connected to an Edale model C thermometer. The thermistor protruded 1 cm from the earmould and did not touch the tympanic membrane. The ears were insulated using foam pads secured to the head by adjustable elastic straps. Thermistors were placed on the chest over pectoralis major, lateral aspect of arm, mid-anterior thigh and lateral aspect of leg to measure skin temperature every 5 min. The temperatures at these sites were used to calculate mean skin temperature using the formula of Ramanathan (1964).

Measurement of respiratory gas exchange

Respiratory gas exchange was measured at 5 or 10 min intervals by collection of the subjects' expired air into 50 l Douglas bags using a low resistance mouthpiece and corrugated plastic tubing. Gas volume was measured using a dry gas meter calibrated against a Tissot spirometer. The gases were analysed for oxygen fraction using a paramagnetic analyser (Taylor Servomex, Model OA 272) and for carbon dioxide fraction using an infrared capnograph (Gould, Mark 2). The measurements of oxygen content and volume were used to calculate heat production using the formula of Weir (1949).

Measurement of sweat evaporation

Sweat evaporation rate was measured, at 10 min intervals, on the anterior chest and lateral aspect of thigh, using the principle of the ventilated measuring cup. Air was drawn through the cup at 1.5 l min^{-1} by a diaphragm pump (Charles Austin), and the cup was placed over an area of skin measuring 25 cm^2 . The humidity of the air entering and leaving the cup was measured by dew point sensing elements (Michell Instruments). The difference in humidity between incoming and outgoing air was used to derive evaporative water loss from the skin (Lamke & Wedin, 1971; Ayling, 1986).

Statistics

Data are expressed as mean $\pm$ s.e. mean and results were examined using Wilcoxon's matched pairs signed rank test or one-way analysis of variance for correlated data, followed by the Tukey test for the comparison of means.

Results

There were no significant differences in resting and peak heat production (Table 1), derived from oxygen consumption (Figure 1).

Table 1 Mean (s.e. mean) resting (after placebo or drug) and peak (after exercise) heat production in the saline placebo (S), glycopyrrolate (G) and atropine (A) groups

		S	G	A
Heat production (kJ min ⁻¹)	Rest	6.07 (0.74)	4.76 (0.68)	5.41 (1.22)
	Peak	24.31 (4.22)	25.64 (4.22)	20.87 (5.39)

Figure 1 Effect of saline placebo (○), glycopyrrolate (◐) and atropine (●) on oxygen consumption after exercise (mean $\pm$ s.e. mean, $n = 5$).

Sweat evaporation rate increased following exercise in all subjects (Figure 2). Evaporation rate from the thigh was higher after saline placebo compared with atropine both immediately, and 10 min after exercise ($P < 0.01$). Evaporation rate from the chest was higher after saline placebo compared with atropine immediately after exercise ($P < 0.05$). There were no significant differences in sweat evaporation from either site between atropine and glycopyrrolate; nor between saline placebo and glycopyrrolate. If peak sweat evaporation rate is examined for each individual it can be seen that atropine always reduced sweat evaporation when compared with saline placebo

(Figure 3). In contrast glycopyrrolate did not always attenuate sweat evaporation compared with saline placebo; in subjects 1 and 4 the rate of sweat evaporation from the chest was not significantly altered by glycopyrrolate. These individual differences are not apparent from the mean values. Evaporation rates from both sites had returned to baseline levels 20 min after exercise.

Mean skin temperature decreased for 15 min after exercise following saline placebo, but not after either drug (Figure 4). Mean peak rises in skin temperature occurred 45 min (saline) and 30 min (atropine and glycopyrrolate) after exer-

Figure 2 Effect of saline placebo (○), glycopyrrolate (●---●) and atropine (●—●) on sweat evaporation rate from the thigh and chest after exercise (mean $\pm$ s.e. mean, $n = 5$).

Figure 3 Peak sweat evaporation in individual subjects during the three studies. ▨ saline, □ glycopyrrolate, ▤ atropine.

cise. There were no significant differences between the studies in mean skin temperature after any agent.

There were no significant differences in the increase in core temperature after exercise between the drug and saline placebo groups (Figure 5). Core temperature had returned to baseline in all studies by 45 min after exercise.

Discussion

The method of Wada (1950), involving counting iodine stained starch granules on the skin surface, has been widely used to measure sweat production. During the present study, sweat evaporation rate was measured. This is a more important factor in thermoregulation, because heat is lost only when sweat actually evaporates from the skin. Skin temperature reflects sweat evaporation rate and, following saline placebo, skin temperature initially fell after exercise, in association with sweating. This resembles the pattern normally seen during body heating

(Lamke & Wedin, 1971). In contrast, following glycopyrrolate and atropine, skin temperature did not show an initial fall after exercise, reflecting an overall smaller sweating response to exercise compared with the saline study.

The doses of anticholinergic drugs used in the present study were chosen because they have been suggested to be equipotent for inhibition of sweating (Mirakhur & Dundee, 1980). Although there were no significant differences between the sweating responses after atropine or glycopyrrolate, the differences in sweating between saline placebo and atropine and saline placebo and glycopyrrolate are not consistent with an equipotency of 0.015 mg kg⁻¹ atropine and 0.003 mg kg⁻¹ glycopyrrolate. Individual variation in inhibition of sweating after the drugs may explain the failure to show equipotency with these doses.

In the present study heat production and change in core temperature after exercise were no different following saline placebo or anticholinergic drugs. To account for this, the com-

Figure 4 Effect of saline placebo (○), glycopyrrolate (●---●) and atropine (●—●) on change in skin temperature after exercise (mean $\pm$ s.e. mean, $n = 5$).

Figure 5 Effect of saline placebo (○), glycopyrrolate (●---●) and atropine (●—●) on change in core temperature after exercise.

bination of evaporative and non-evaporative heat loss must also have been the same in all three groups. However, as it has been shown that evaporative heat loss was less following anticholinergic drugs compared with saline placebo, the non-evaporative heat loss must have been greater after drug treatment to account for the fact that the change in core temperature following anticholinergic drugs was no different to that seen following saline placebo.

It is therefore suggested that reduction in sweating following clinical doses of atropine and

glycopyrrolate is compensated for by increased non-evaporative heat loss, preventing significant elevation in core temperature in response to increased heat production after exercise.

The authors are very grateful to the volunteers and to Dr P. J. Halsall, Mrs E. Hay, and Mr P. Allam for technical assistance during the studies. The atropine and glycopyrrolate were kindly supplied by Mr C. Jones, A. H. Robins Ltd.

References

- Åstrand, P. O. & Rodahl, K. (1977). *Textbook of Work Physiology*, 2nd edn, pp. 344–345. New York: McGraw-Hill Book Co.
- Ayling, J. H., Simpson, K. H., Ellis, F. R., Halsall, P. J., Hay, E. E. & Allam, P. L. (1986). Influence of glycopyrrolate and atropine on thermoregulation after exercise. *Br. J. Anaesth.*, **57**, 804P.
- Ayling, J. H. (1986). Use of dew-point temperature sensors for intermittent measurements of sweat production and evaporation rates. *J. Sports Med. Physical Fitness*, (in press).
- Cullumbine, H. & Miles, S. (1955). The effect of atropine sulphate on men exposed to warm environments. *Q. J. Exp. Physiol.*, **41**, 162–179.
- Lamke, L. O. & Wedin, B. (1971). Water evaporation from normal skin under different environmental conditions. *Acta Derm. Venereol. (Stockholm)*, **51**, 111–119.
- Mirakhor, R. H. & Dundee, J. W. (1980). A comparison of the effects of atropine and glycopyrrolate on various end organs. *J. Roy. Soc. Med.*, **73**, 727–730.
- Ramanathan, N. L. (1964). A new weighting system for mean surface temperature of the human body. *J. appl. Physiol.*, **19**, 531–533.
- Stoll, H. C. (1948). Pharmacodynamic considerations of atropine and related compounds. *Am. J. med. Sci.*, **215**, 577–592.

- Wada, M. (1950). Sudorific action of adrenaline on the human sweat glands and determination of their excitability. *Science*, **111**, 376–377.
- Weir, V. de J. B. (1949). New methods for calculating metabolic rate with special reference to protein metabolism. *J. Physiol.*, **109**, 1–9.

(Received 20 May 1986,
accepted 26 July 1986)