EFFECTS OF LOW CONCENTRATIONS OF CYCLOPROPANE AND HALOTHANE ON PEAK VELOCITY OF SACCADIC EYE MOVEMENTS

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SUMMARY
We have investigated the effect of 4.7 and 8.8% MAC of cyclopropane, and 5.3 and 9.3% MAC of halothane on the peak velocity of saccadic eye movements (PSV) in six healthy volunteers. Both concentrations of cyclopropane and halothane significantly depressed PSV (P < 0.01) compared with air, in a dose-related fashion. Halothane depressed PSV significantly more than cyclopropane (P < 0.05). PSV returned to baseline within 5 min after discontinuation of the agents. There was no significant difference between cyclopropane, halothane and air in subjective assessment of sedation.

KEY WORDS

Saccadic eye movements are the fastest movement of which the oculomotor system is capable. The peak velocity of saccadic eye movement (PSV) is thought to be an indicator of the functional state of a well defined group of neurones in the brainstem reticular formation [1] and, besides being a sensitive indicator of CNS depression, has the advantage of being beyond voluntary control [2]. In a previous study [3], 5 and 10% MAC of isoflurane were found to depress PSV, whereas the effects of equi-MAC concentrations of nitrous oxide were indistinguishable from those of air. One hypothesis to explain the difference between the agents is the sympathetic stimulating effect of nitrous oxide [4, 5]. Cyclopropane has a similar stimulating effect [6, 7]. We have therefore investigated this hypothesis by comparing the effect on PSV of 5% and 10% MAC concentrations of cyclopropane with halothane, an agent generally regarded as similar to isoflurane [8].

The aims of this study were to determine if 5% and 10% MAC concentrations of cyclopropane and halothane affect PSV, if these effects were the same for both agents and if there was a dose–effect relationship.

SUBJECTS AND METHODS
We studied six drug-free healthy volunteers, aged 21–33 yr. Informed consent was obtained from each subject and the study was approved by the local Ethics Committee. The study consisted of three treatment sessions given at intervals of 1 week or greater. Each session consisted of assessment while breathing air or 5% and 10% MAC concentrations of one of the test agents. The agents were administered in a random order determined by opening the next envelope in a pregenerated set of six sets of the three sequences. Each volunteer was allowed to practise the saccadic eye movement task before the formal sessions until there was no learning effect.

Breathing system
Concentrations of 0.5–1% cyclopropane in air were delivered by a Boyle anaesthetic machine with a total fresh gas flow of 12 litre min⁻¹. Concentrations of 0.05–0.14% halothane were delivered using a calibrated Fluotec 3 vaporizer.

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and diluting the output concentrations with air via a second calibrated flowmeter with a total fresh gas flow of 12–22 litre min⁻¹. The inspiratory concentrations were adjusted to maintain as near as 5% and 10% MAC of end-tidal concentrations as possible (0.46 and 0.92% cyclopropane; 0.038 and 0.076% halothane [9]), based on the NARKUP computer program [10] adjusted for the subject's age, sex, height and body weight. In the case of halothane, overpressure was applied for 10 min by giving approximately 2–2.5 times the required concentration and this was followed by the maintenance concentration for 20 min.

The breathing system is shown in figure 1. An Ambu valve was inserted into the inspiratory limb of the breathing system to avoid the expired gas being diluted by excess fresh gas. Each volunteer wore a Royal Air Force pilot’s face mask with non-rebreathing valves. Two fine bore tubes were attached to the mask and alveolar gas samples were taken through one tube at 10-min intervals just before each PSV measurement. Expired carbon dioxide was monitored continuously with a Normocap 200 infra-red analyser through the other sample tube to identify the alveolar plateau. Cyclopropane and halothane concentrations were measured by gas-liquid chromatography calibrated by standard gas mixtures. Halothane standards in the range 0.02–0.2 vol% were prepared in gas-tight glass jars of known volume using a weighed aliquot of liquid halothane and treating the vapour as if it were an ideal gas. In the case of cyclopropane, a calculated volume of pure gas was taken from a Boyle anaesthetic machine by a syringe to obtain standards between 0.5 and 1 vol%.

**Saccadic eye movement measurements**

Complete details of the eye movement recording system have been reported in two previous
papers [3, 11]. In brief, saccades were generated by requiring the subject to follow the horizontal movements of an illuminated target. An IBM compatible (Opus PC II) microcomputer controlled the target movements (fig. 1). The target was moved every 1.5 s instantaneously in a predetermined pattern designed to generate 24 analysable saccades at symmetrical eye displacements of 10°, 20°, 30° and 40°. Three such sequences were taken with 20-s intervals at each measurement point.

Eye position was monitored from the electro-oculogram (EOG), which was measured from stick-on silver-silver chloride electrodes placed lateral to both outer canthi, and a reference electrode on the forehead (fig. 1). Electrode resistances were always less than 4 kΩ. The EOG was d.c. amplified, low-pass filtered (-3dB at 50 Hz) before being digitized to 12-bit resolution at a sampling frequency of 250 Hz and stored on disk.

Saccades were analysed in two stages according to the method of Marshall and Richens [12]. The digitized data from each target displacement were first processed to locate saccades. Each saccade was analysed to extract the size of the saccade in degrees and the PSV in degrees per second. Few saccades are completely accurate and so the size of the saccade may be greater (overshoot) or less (undershoot) than the target displacement. Because peak velocity is determined by the size of the saccade and not the size of the target displacement, it is necessary to model the velocity–saccade size relationship and calculate the velocity achieved for a defined saccade size. Saccades show a unique feature: the greater the angular eye movement up to about 30–35°, the greater the peak velocity. Therefore the relationship between the degree of eye displacement and PSV was modelled for each measurement occasion, by fitting a quadratic curve to the displacement–velocity relationship. The interpolated value at 35° was taken as the measure in this study (fig. 2). (There is always greater variability in the displacement–velocity points with volatile agents than with air, and this variability increases with increasing concentrations. At concentrations greater than those used in this study, the combination of increased variability and "missed" values renders the measurement of PSV unreliable.)

Each session started with a 15-min baseline period with the subject breathing air, followed by 30 min each of approximately 5% and 10% MAC and 10 min for recovery breathing air. PSV was measured at 5-min intervals during the baseline period, at 10-min intervals during the inhalation of 5% and 10% MAC and once during the recovery period. An additional measurement was made after a 15-min break without the face mask. All the PSV measurements were normalized by dividing the values by the mean of the baseline measurements on that treatment day. These normalized PSV values at 15 and 25 min at each anaesthetic concentration were averaged and the means were compared with control air values by Student's two-tailed t test. As the study was designed to answer specific questions, a multiple comparisons correction was not applied [13].

Subjective assessments
Each subject was asked to assess their degree of sedation by marking a 10-cm linear analogue scale each time just before the PSV measurements. The extremes were denoted as "wide awake" and "just before falling asleep". All visual analogue scores (VAS) were normalized by subtracting the mean of the baseline measurements on that day. Wilcoxon's rank sum test was applied to normalized VAS. Subjects were also asked about the presence or absence of odour, headache and nausea at the end of each treatment, and Fisher's test of exact probability was applied to the responses.

RESULTS
The normalized PSV values at 35°, the visual analogue scores and the end-tidal concentrations of cyclopropane and halothane are plotted in figure 3. Mean end-tidal concentrations of cyclopropane were 4.7 (SEM 0.3)% and 8.8 (0.8)% of MAC and those of halothane were 5.3 (0.5)% and 9.3 (0.5)% of MAC, respectively, at 15 and 25 min of each session. End-tidal concentrations of carbon dioxide were always in the range 4–5% with each concentration of each agent. Both cyclopropane and halothane caused a highly significant (P < 0.01) dose-related depression of PSV. Depression of PSV by halothane was significantly greater than that caused by cyclopropane (P < 0.05) (fig. 3). To correct for the actual concentrations not being exactly 5 or 10% of MAC, the grand mean of all concentrations of both agents was calculated and found to be 7.0 (0.5)% of MAC. The PSV values
for each agent were interpolated for this concentration. Cyclopropane caused an 88.9 (1.4) % reduction in normalized PSV and halothane a 82.0 (2.2) % reduction (fig. 4) \( (P < 0.05) \). PSV had returned to baseline values within 5 min of discontinuation of the anaesthetic agents. End-tidal concentrations at this time were 2.1 (0.4) % of MAC for cyclopropane and 3.0 (0.7) % of MAC for halothane. There was no significant differences in VAS between air and either cyclopropane or halothane (fig. 3). Subjective assessment of the appreciation of odour, the feeling of nausea and headache under each treatment are shown in table I. The only significant difference between the agents was detection of odour between halothane and air.

Our results show that both cyclopropane and halothane caused dose-dependent depression of PSV and that depression with halothane was significantly greater than with cyclopropane at equivalent sub-anaesthetic concentrations.

The brain tension of cyclopropane quickly equilibrates with a constant inspired tension because of the low solubility of cyclopropane in blood and brain tissue. This is not true of halothane. The NARKUP computer program [10] was run with the same profile of inspired concentrations as in the experiment, and the values of brain and alveolar tension were computed at 15 and 25 min and averaged. The computed alveolar concentrations were in good agreement with the measured values (table II).
Therefore the brain tension in MAC units was estimated for each subject from the individual measured alveolar concentrations and the computed brain:alveolar tension ratio (table II). Accordingly, the averages of normalized PSV at 15 and 25 min could be compared for each session.

The end-tidal concentrations of both agents were smaller than the target concentrations of 5% and 10% MAC, mainly because we were not able to monitor end-tidal concentrations continuously.

VAS for sedation failed to differentiate both cyclopropane and halothane from air. Two of six subjects showed improvement in VAS for sedation while alveolar concentrations were increasing, although PSV was progressively depressed. This suggests that subjective assessments are an unsatisfactory indicator of mild CNS depression, a conclusion reached by Gao, Marshall and Vickers for isoflurane [3], and by Gao, Mapleson and Vickers for propofol [11].

Although direct comparisons are not possible, this study, using identical methodology and many of the same volunteers, found that halothane had effects identical to those of isoflurane at almost equi-sub-MAC concentrations [3]. However, cyclopropane was not similar to nitrous oxide, but produced an intermediate effect. The similarity between halothane and isoflurane is not unexpected [8]. Although both cyclopropane and nitrous oxide have a sympathetic stimulating effect [4-7] the lesser depression by cyclopropane compared with halothane and isoflurane supports the conclusion that a sympathetic stimulating effect may be relevant to this difference from nitrous oxide. The results do not, however, explain why equi-sub-MAC concentrations of halothane and isoflurane have comparable and marked effects, nitrous oxide has no detectable effect and cyclopropane has an intermediate effect on PSV. This is further confirmation that it is too simplistic to think that equi-MAC concentrations of inhalation agents have equivalent actions throughout the CNS.

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REFERENCES


