Psychomotor and cognitive effects of 15-minute inhalation of methoxyflurane in healthy volunteers: implication for post-colonoscopy care

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Background and study aims: Colonoscopy with portal inhaled methoxyflurane (Penthrox) is highly feasible with low sedation risk and allows earlier discharge. It is unclear if subjects can return to highly skilled psychomotor skill task shortly after Penthrox assisted colonoscopy. We evaluated the psychomotor and cognitive effects of 15-minute inhalation of Penthrox in adults.

Patients and methods: Sixty healthy volunteers (18 to 80 years) were studied on 2 occasions with either Penthrox or placebo in a randomized, double-blind fashion. On each occasion, the subject's psychomotor function was examined before, immediately, 30, 60, 120, 180 and 240 min after a 15-minute inhalation of studied drug, using validated psychomotor tests (Digit Symbol Substitution Test (DSST), auditory reaction time (ART), eye-hand coordination (EHC) test, trail making test (TMT) and logical reasoning test (LRT).

Results: Compared to placebo, a 15-minute Penthrox inhalation led to an immediate but small impairment of DSST ($P<0.001$), ART ($P<0.001$), EHC ($P<0.01$), TMT ($P=0.02$) and LRT ($P=0.04$). In all subjects, the performance of all 5 tests normalized by 30 minutes after inhalation, and was comparable to that with placebo. Although increasing age was associated with a small deterioration in psychomotor testing performance, the magnitude of Penthrox effects remained comparable among all age groups.

Conclusions: In all age groups, a 15-minute Penthrox inhalation induces acute but short-lasting impairment of psychomotor and cognitive performance, which returns to normal within 30 minutes, indicating that subjects who have colonoscopy with Penthrox can return to highly skilled psychomotor skills tasks such as driving and daily work the same day.

Introduction

Methoxyflurane is a halogenated ether that was used extensively for general anesthesia in the early 1960s [1]. At low dose, methoxyflurane exerts a uniquely powerful analgesic property without significant sedative effects [1–3]. This allows portable inhaled methoxyflurane (Penthrox, 3 mL per inhaler) to be used as a preferred analgesic in the Australasian community by ambulance services in the pre-hospital setting to provide pain relief without the need for an intravenous (IV) cannula [4–6]. Recently, methoxyflurane has also been increasingly used as analgesia for wound dressing for burn patients [7], prostate and bone marrow biopsy [8,9], computed tomography enteroclysis [10], and colonoscopy [2,3]. To date, the use of methoxyflurane at current dosage (up to 6 mL per day) has a good safety profile in over 5 million patients [11].

In a recent large randomized trial, patients (n=125) who were given a methoxyflurane inhaler during colonoscopy experienced good analgesia, liked being able to control drug administration, and found that methoxyflurane inhaler was pleasant and easy to use, as compared to patients who were sedated with midazolam and fentanyl (n=126) [2]. Endoscopists who performed colonoscopies on patients who used a methoxyflurane inhaler found patients were more cooperative and had better postprocedure recall. Furthermore, the use of methoxyflurane was associated with a shorter recovery time (by at least 15 minutes), with no sedative effect or incidence of respiratory depression [2,3]. The potential clinical implication of these findings is that the use of methoxyflurane, instead of sedation for colonoscopy in clinical practice, can lead to earlier discharge and thus facilitate the workflow of endoscopy units.

An unanswered issue related to the use of methoxyflurane in clinical settings is its impact on psychomotor function and the ability to drive or perform complex tasks, as the lack of adverse psychomotor effects from methoxyflurane may allow patients to drive, and even return to work on the day of colonoscopy. Given that colonoscopies are increasingly being performed for screening and surveillance purposes, the ability to return home or to work without carers would carry significant cost benefit and minimize work disruption. Currently, there are no data on the impact of inhaled methoxyflurane, or methoxyflurane in general, on the psychomotor function of humans. As there are no appropriate measures of within-subject variation and that information is not available from other published studies, the aims of this study were to evaluate the effects of inhaled methoxyflurane on psychomotor functions of healthy volunteers and the impact on psychomotor function in the aging after inhalation of methoxyflurane.

Patients and methods

Subjects

Sixty (n = 60) healthy volunteers who were able to give informed consent, able to understand adequately use of the methoxyflurane (Penthrox) inhaler, and who had no contraindication to use of methoxyflurane were recruited. To assess the effects of methoxyflurane on different age groups, it was deemed necessary to have "equal representation" of subjects in different age groups, with 10 subjects per group arbitrarily divided as follows: 18 – 30 years; 31 – 40 years; 41 – 50 years; 51 – 60 years; 61 – 70 years and 71 – 80 years. Exclusion criteria were: (1) a history of significant alcohol (> 40 g/d for males, 20 g/d for females) or narcotic use; (2) previous history of significant liver, cardiac or respiratory illnesses (i. e. ischemic heart disease, chronic obstructive pulmonary disease, chronic liver disease); (3) body mass index less than 19 kg/m^2; (4) any renal impairment; (5) previous possible allergy to the medication by the patient or a relative; (6) hypersensitivity to fluorinated agents; (7) previous head injury; (8) difficulty in following instructions (including language barrier); (9) concurrent use of any potential nephrotoxic drugs (e. g. aminoglycosides) or tetracyclines; and (10) personal or family history of malignant hyperthermia. Subjects were withdrawn from the study if they experience an adverse event or wished to discontinue.

The subjects were screened for suitability for the study based on the inclusion/exclusion criteria, either by in-person consultation or via a telephone conversation. Those who met the entry criteria were asked to have a screening visit for a blood test (4 mL) to check renal (urea and creatinine) and liver function. Only subjects who had normal renal and liver function were included in the study. Women of childbearing age were tested for pregnancy using a urine sample prior to commencement of the study, and excluded if they were pregnant. Adequate vision (with correction by glasses) was assessed by the 6-m reading test and normal was defined as 6/6 vision. Prior to involvement in the study, each subject was also asked to attend the Audio-Clinic Adelaide for a formal hearing test. For subjects between ages 71 and 80, a mini-mental test was performed as a screen for any overt cognitive impairment. Those with score less than 24 were excluded.

The study was approved by the Human Research Ethics Committee and written informed consent was obtained from each subject prior to inclusion.

Study protocol

Healthy volunteers were evaluated in a randomized, placebo-controlled, crossover manner. Each subject was studied on 2 occasions with either placebo or methoxyflurane, separated by at least a 1-week duration and the order was randomized. Although "placebo" consisted of 3 mL of normal saline, the solution had the smell of methoxyflurane to "blind" the subject from distinguishing placebo from active methoxyflurane. Prior to the trial, a training session for the psychomotor tests was given to each subject, to minimize learning effects.

Randomization of the order of the studied drug and placebo was done in blocks of 10 using a computer program (GraphPad Software Inc., La Jolla, CA, USA). Results of the randomization were enclosed in envelopes labelled from subjects 1 to 60. After successful recruitment, an envelope with a randomization letter was opened by an investigator who was not participating in the test delivery. The studied drug was prepared by this investigator, which was then given to the investigator who was administering the drug and tests, in a blinded fashion. The results of randomization were not revealed until the study was completed.

On each study occasion, subjects were studied in the morning and asked to not have any alcohol, illicit drugs or medications that could influence psychomotor function during the preceding 5 days. Subjects were also asked to have no more than 2 cups of tea or coffee, and not to have energy drinks or to take over-the-counter remedies with stimulant effects (such as pseudofat), during the 24 hours prior to the study. A battery of tests were then conducted to assess the subjects' psychomotor function at baseline (t = – 15 minutes). The subjects were then asked to inhale through a portable green inhaler containing either 3 mL of saline (placebo) or methoxyflurane over 15 minutes. The subjects were asked to take 10 inhalations of methoxyflurane at the beginning and 1 inhalation every 3 breaths thereafter for the rest of the 15-minute duration. The "15-minute duration" was chosen, as that was the mean total colonoscopy time reported in our previous studies [2, 3]. Psychomotor assessment was conducted immediately after (t = 0 minutes), 30 minutes, 60 minutes, 120 minutes, 180 minutes and 240 minutes after the 15-minute inhalation.

Psychomotor assessment

A battery of 5 tests was used, all which had been previously validated and used extensively to assess psychomotor function of medications with analgesic and sedative properties. The tests included visual scanning, auditory reaction time, eye-hand coordination, mental flexibility, sustained attention, speed of information processing and memory [12 – 14].

1. The ***Digit Symbol Substitution Test*** (DSST), which assesses a number of different functions, including visual scanning, mental flexibility, logic reasoning, sustained attention, psychomotor speed, and speed of information processing [15 – 17], was a 1-minute test that required the subject to replace digits with corresponding symbols according to a digit-symbol code listed on the top of the paper [16]. The dependent measures were total number of symbols drawn and number of symbols drawn correctly.
2. The computerized ***logical reasoning test*** (LRT) consisting of true-false statements about the juxtaposition of the two letters A and B (e. g., A is preceded by B – true or false). The 1-miniute test assessed higher mental processes such as reasoning, logic, and verbal ability [18]. The dependent

Table 1 Summary of the demographics and baseline characteristics of subjects.

	Ages 18 – 30	Ages 31 – 40	Ages 41 – 50	Ages 51 – 60	Ages 61 – 70	Ages 71 – 80
Mean age	22.8 ± 1.0	34.5 ± 0.9	44.2 ± 0.9	56.5 ± 0.9	64.3 ± 0.8	76.3 ± 1.0
Gender	5 M : 5 F	3 M : 7 F	7M : 3F	5 M : 5 F	9 M : 1 F	7 M : 3 F
% with normal visual acuity	100 %	100 %	100 %	100 %	100 %	100 %
% with normal hearing	100 %	100 %	100 %	100 %	100 %	100 %

measures were the total number of statements answered and number of statements answered correctly.

3. The 1-minute ***auditory reaction time*** (ART) test measures the time it took for subjects to react to 10 50-dBA computer-generated tones that were delivered at random time intervals [19]. The mean reaction time (in seconds) to depress a computer keyboard spacebar was the dependent measure.
4. The 1-minute ***eye-hand coordination*** (EHC) test requires the subject to track a randomly moving target (a circle) on the computer screen using a computer mouse [19]. The dependent measure was the duration of times that a small plus sign, which was controlled by the mouse, correctly followed the target circle, within 1 cm from the center of the circle.
5. The ***Trail Making Test*** (TMT) is primarily a test of motor speed and visual attention. In the first part, the subject's task is to quickly draw lines on a page connecting 25 consecutive numbers. In the second part, the subject must draw lines alternating between numbers and letters [20]. The dependent measure is the time it took for a person to connect all the letters and numbers in the correct order.

Measured outcomes

Primary endpoints were: (1) the differences in psychomotor functions between inhaled methoxyflurane and placebo in healthy volunteers; and (2) the intra-subject and inter-subject variability in these outcomes for planning a definitive equivalence study.

Secondary endpoints were: (1) the duration and severity of adverse impact of inhaled methoxyflurane on psychomotor functions in healthy volunteers; and (2) the influence of age on the effects of methoxyflurane on the psychomotor function in healthy subjects.

Data analysis

Data are expressed as mean (± standard deviation (SD). Fisher's exact test was used for comparison of categorical data, and independent Student *t*-test for continuous data. The differences in psychomotor scores between methoxyflurane and placebo at different time points were compared using ANOVA analysis. Similarly, the differences over time between methoxyflurane and placebo were compared by ANOVA analysis. Analyses was performed using GraphPad Prism statistical software, version 6 (GraphPad Software Inc., La Jolla, CA, USA). A *P* value less than 0.05 was accepted as indicating statistical significance.

Results

Sixty subjects were successfully studied over 12 months and the trial ended after the target number of volunteers was reached. The characteristics of the subgroups are summarized in **Table 1**. All subjects tolerated inhalation of placebo and methoxyflurane without any adverse events. There were no differences in the baseline assessments of DSST, ART, EHC, TMT, and LRT (**Fig. 1**) prior to methoxyflurane and placebo inhalation. Compared to placebo, a 15-minute methoxyflurane inhalation led to an immediate modest impairment of DSST ($P<0.001$), ART ($P<0.001$), EHC ($P<0.01$), TMT ($P=0.02$) and LRT ($P=0.04$). While there were no significant changes in results of the DSST, ART, EHC and TMT tests between baseline and immediately after placebo, performances on the tests immediately after methoxyflurane were poorer than those at baseline (**Table 2**). For the LRT test, although the number of correct answers immediately after inhaled methoxyflurane was unchanged, the performance after placebo was better with significantly more correct answers (**Table 2**). In all subjects, performance on all 5 tests normalized by 30 minutes after cessation of inhalation, and was comparable to that for placebo.

Increasing age was associated with a small deterioration in performance of psychomotor function tests. Except for hearing, the effects of methoxyflurane on other psychomotor functions remained comparable among all age groups (**Fig. 2**). The magnitude of methoxyflurane's effect on hearing was greater in the subjects older than age 60 and most pronounced immediately after inhalation of methoxyflurane. In all subjects, hearing returned to baseline by 30 minutes after inhalation.

Discussion

Despite increasing use of inhaled methoxyflurane in clinical medicine, this is the first study that examined the effects of short-term use of methoxyflurane on psychomotor functions in humans. The current study demonstrated that 15-minute inhalation of methoxyflurane in healthy volunteers led to a small, acute deterioration in all aspects of psychomotor function but the effects lasted for less than 30 minutes after inhalation, and *e*xcept for auditory reaction time, the psychomotor impact of methoxyflurane was equally observed in all age groups. Except for the DSST test, inhaled methoxyflurane induces an approximately 10% reduction in performance of highly skilled psychomotor tasks. Together our data indicated that subjects who use inhaled methoxyflurane as a mode of conscious analgesia for outpatient procedures such as colonoscopy or bone marrow or prostate biopsy can safely return the same day to tasks that require high psychomotor skills, such as driving and working.

Current recommendations from the British and ANZ Colleges of Anaesthetists are that after undergoing general anesthesia or IV sedation, a patient should not drive a car for 24 hours [21]. Driving is a complex task, and involves attention, information processing, judgement, sensorimotor skills, and perception [22]. Fitness to drive is assessed by psychomotor function tests, multiple sleep latency tests, and simulated driving tests [23]. Of these, psychomotor function tests are most commonly used to assess the "recovery time" for the subject's functions to return to baseline levels [23]. Tracking tasks, the pegboard test, the Maddox wing

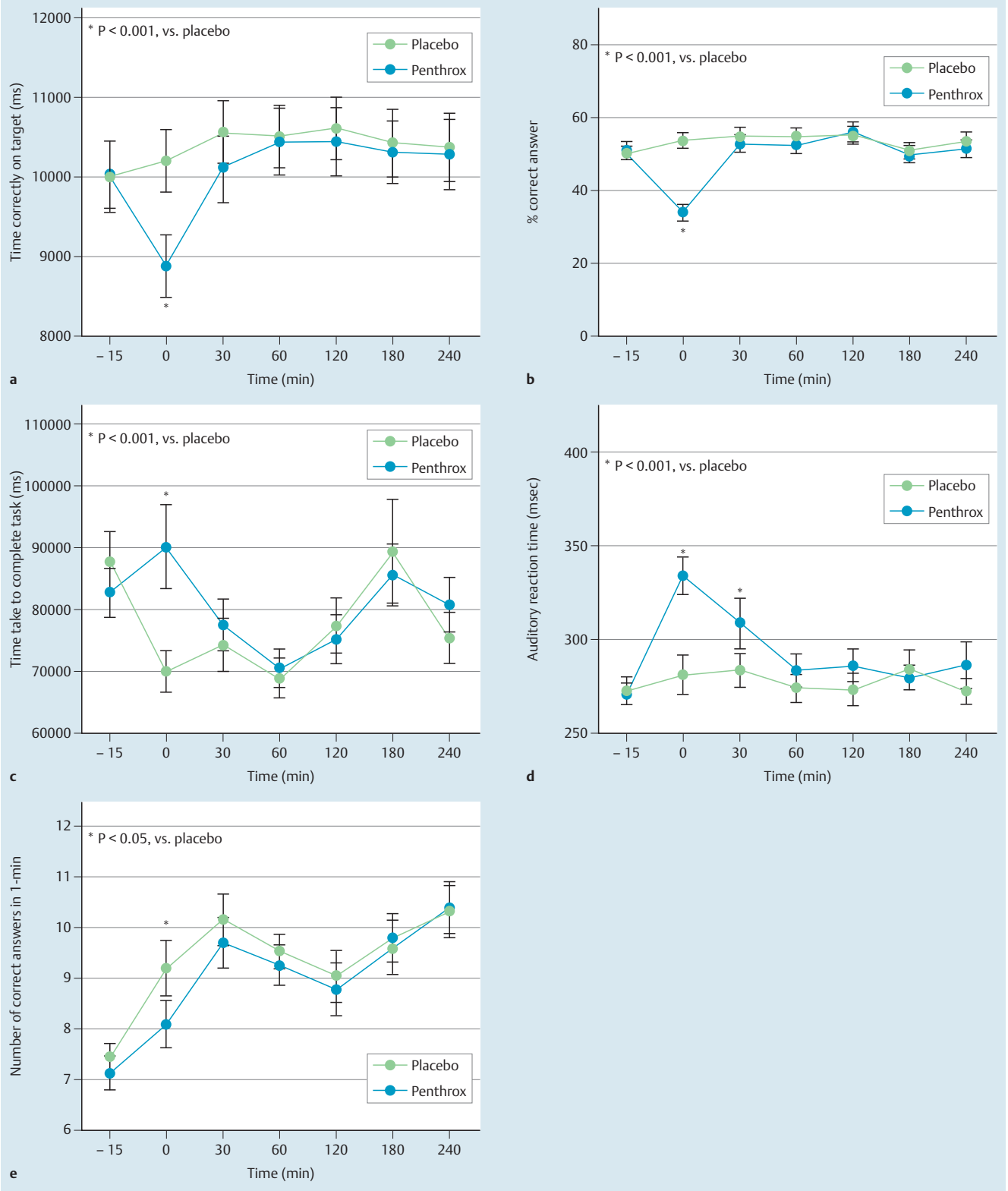

Fig. 1 Comparison of the overall effects of 15-minute inhaled methoxyflurane over placebo on **a** 1-minute eye-hand coordination (EHC); **b** Digital Symbol Substitution Test (DSST); **c** Trail Making Test (TMT); **d** 1-minute auditory reaction time (ART); and **e** logical reasoning test (LRT).

test, and perceptive accuracy tests appear to be the most sensitive psychomotor tests [23], all of which are included in the current study. Performance on psychomotor function testing has been shown to correlate with outcomes of driving simulation tests, which has been used as the gold standard to assess fitness to drive [22,23]. Based on these assessments, the longest psychomotor recovery time period after administration of IV midazolam (maximum dose 0.15 mg/kg) is 10 hours [24–26], fentanyl (maximum dose 2.5 mcg/kg) is 6 hours to 8 hours [27,28], combination of propofol/midazolam/fentanyl is 8 hours to 10 hours [29, 30] and propofol alone is 2 hours [31]. These are the most commonly used IV sedative agents for colonoscopy, and thus, provid-

	Baseline	Immediately after drug administration	% change from baseline measurements	*P* value
Inhaled methoxyflurane				
DSST (no. correct answer in 2 min)	31.1 ± 2.5	18.8 ± 4.7	− 34.4 ± 17.2 %	*P* < 0.0001
ART (msec)	301.3 ± 23.4	368.2 ± 16.9	+ 26.5 ± 7.0 %	*P* < 0.0001
EHC (time on target, msec)	5342 ± 829	4603 ± 713	− 9.3 ± 6.2 %	*P* < 0.0001
TMT (time taken to connect numbers and letters, sec)	83.3 ± 3.8	92.6 ± 3.6	+ 12.4 + 4.0 %	*P* = 0.02
LRT (no. correct answer in 1 min)	7.2 ± 0.3	7.7 ± 0.4	+ 6.2 ± 3.8 %	*P* = 0.21
Placebo				
DSST(no. correct answer in 2 min)	31.4 ± 2.3	34.5 ± 4.9	+ 3.4 ± 6.2 %	*P* = 0.74
ART (msec)	299.3 ± 20.5	305.9 ± 19.3	+ 3.2 ± 3.9 %	*P* = 0.68
EHC (time on target, msec)	5491 ± 1036	5921 ± 897	+ 4.3 ± 5.1 %	*P* = 0.09
TMT (time taken to connect numbers and letters, sec)	83.8 ± 4.1	78.1 ± 3.4	− 6.8 + 2.8 %	*P* = 0.15
LRT (no. correct answer in 1 min)	7.3 ± 0.3	8.9 ± 0.5	+ 28.3 ± 7.7 %	*P* < 0.0001

Table 2 Immediate impact of studied drugs on the performance of psychomotor tests in healthy volunteers.

DSST, Digital Symbol Substitution Test; ART, 1-minutes auditory reaction time; EHC, 1-minutes eye-hand coordination; TMT, Trail Making Test; LRT, logical reasoning test

ing a possible explanation for the recommendations not to drive for 12 to 24 hours after IV sedation, depending on the countries [32]. In our study, we have demonstrated that the longest psychomotor recovery time after administration of inhaled methoxyflurane was 0.5 hour, which is significantly shorter than the currently used IV sedatives. A recent study in Japan demonstrated that, of the 1183 patients who underwent colonoscopy with propofol alone (mean dose of 96.4 [40 – 200] mg) and drove home or to their office after colonoscopy, none had accidents or work incidents during the 24 hours after colonoscopy [31]. Together, our findings suggest that subjects who undergo colonoscopy with inhaled methoxyflurane should be able to drive or return to high-level psychomotor function tasks 1 hour after its administration.

The ability to drive or return to work within a few hours after colonoscopy has major health economic implications. A recent study found that over 90 % of subjects who underwent a screening and surveillance colonoscopy took an average of 2.1 days off work for the procedure and the main reason was for precautionary measures after IV sedation [33]. Furthermore, 50 % of the subjects had friends or family members who took days off from work because of the procedure. Thus, the indirect financial costs to society related to missed work for screening and surveillance colonoscopies should be taken into account, and could be minimized by avoiding use of IV sedation for colonoscopy. In addition to the significantly shorter recovery time from colonoscopy [2, 3], use of inhaled methoxyflurane for colonoscopy can prevent unnecessary time taken off from work and the associated costs to society. In fact, our findings indicate that subjects can return to work within 1 hour after the procedure.

Unsedated colonoscopy, which is a common approach in many countries in Southeast Asia and a few countries in Europe, has a number of other benefits. Even if sedation is safe, it requires an extra nurse and a team educated for monitoring, resulting in higher costs. Furthermore, the requirements for an escort and time burden of recovery from sedation are both barriers to the acceptance of screening colonoscopy. Improved acceptance of colonoscopy is important to allow full use of colonoscopy in cancer screening and prevention. Because most colonoscopies only cause minor discomfort, the procedure can be completed with appropriate analgesia, rather than sedation, in the majority of patients [34, 35]. Undoubtedly, there is a place for unsedated colonoscopy, especially in areas involving screening and surveillance of colonic cancer.

Given that methoxyflurane is a volatile gas, the potential risk of occupational exposure will always be a concern, especially when acute high-dose exposure can lead to transient impairment of highly skilled psychomotor tasks. All available data related to occupational exposure to Penthrox are derived from studies performed in an Ambulance Service setting [1, 11]. Even in the much smaller air space of the ambulance, studies have found that an 8-hour work day exposure is very small (ranging from 0.1 to 0.6 ppm) [11]. Based on 5 million units used in the pre-hospital paramedic setting, such minimal exposure has not been associated with any reported serious adverse events in health care workers [11]. This is in contrast to the inhaled concentration of at least 50 ppm during active inhalation of Penthrox through the mouthpiece [11]. Given that endoscopy rooms are much larger (4 to 5 times the size of the ambulance) and have better ventilation systems, it is expected that the occupational exposure to Penthrox in endoscopy units would be substantially smaller (in the magnitude of 0.001 to 0.01 ppm) than that in the paramedic setting. Furthermore, the new Penthrox inhaler that is currently used in clinical practice has an activated carbon chamber, which can further reduce the concentration of exhaled methoxyflurane. Thus, it is expected that occupational exposure of methoxyflurane and its psychomotor impact on the endoscopic staff would be extremely low, if any. Because methoxyflurane has a characteristic fruity odor, any potential inadvertent leakage can easily be detected and the related adverse exposure readily avoided.

The major strength of the current study is the sample size as well as the inclusion of all appropriate age groups who would be can-

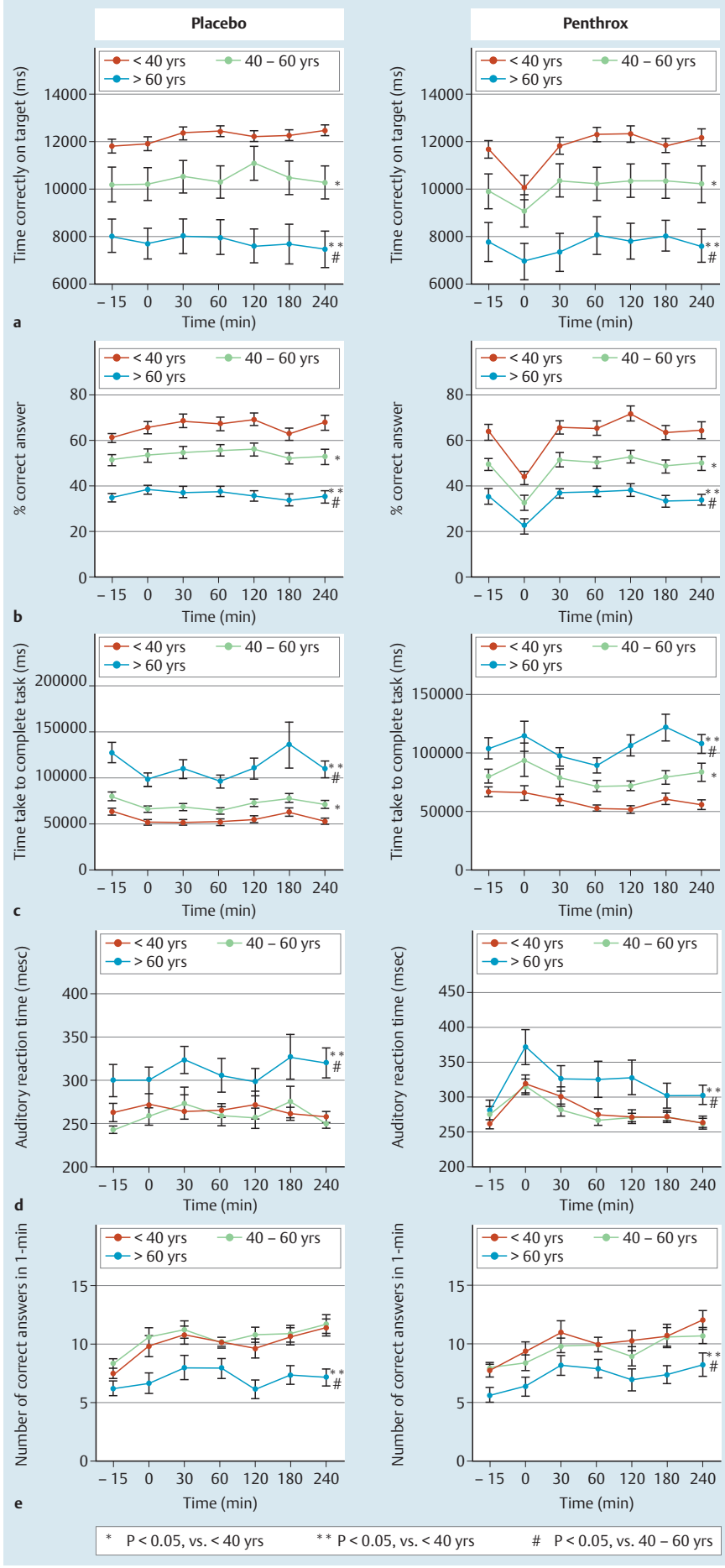

Fig. 2 Impact of inhaled methoxyflurane and placebo, stratifying by age, on **a** 1-minute eye-hand coordination (EHC); **b** Digital Symbol Substitution Test (DSST); **c** Trail Making Test (TMT); **d** 1-minute auditory reaction time (ART); and **e** logical reasoning test (LRT).

didates for screening colonoscopy. However, there are a number of potential weaknesses, including selection bias toward patients who are healthy and with no serious medical conditions such as liver, renal or cardiorespiratory diseases, absence of physiological changes related to bowel preparation, and possibly, absence of sleep deprivation.

Conclusion

In conclusion, a 15-minutes inhalation of methoxyflurane induces an acute but short-lasting impairment of psychomotor and cognitive performance in all age groups, and function returns to normal within 30 minutes after inhalation. These findings indicate that subjects who use inhaled Penthrox for colonoscopy can safely return, the same day, to tasks that require high-level psychomotor skills such as driving and work.

Competing interests: None

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