ALTERATIONS IN PAIN THRESHOLD AND PSYCHOMOTOR RESPONSE ASSOCIATED WITH SUBANAESTHETIC CONCENTRATIONS OF INHALATION ANAESTHETICS IN HUMANS

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SUMMARY
We studied the effects of six inhalation anaesthetics at subanaesthetic concentrations of 0.2 MAC on pain threshold and psychomotor function in six healthy volunteers. When compared with 100% oxygen inhalation, nitrous oxide and methoxyflurane significantly increased pain threshold as measured by a radiant heat algometer, and prolonged the response time to auditory stimuli. In contrast, halothane, enflurane, isoflurane and sevoflurane produced prolongation of the response time to auditory stimuli but did not influence pain perception. The pain threshold with nitrous oxide remained significantly increased 30 min after its discontinuation, while the response time returned to the preinhalation value. We conclude that nitrous oxide and methoxyflurane possess both analgesic and hypnotic actions but halothane, enflurane, isoflurane and sevoflurane do not have an analgesic action at subanaesthetic concentrations, and the analgesic action of nitrous oxide persists after its elimination. (Br. J. Anaesth. 1993; 70: 684–686)

KEY WORDS

General anaesthesia is a result of both analgesic and hypnotic actions of an anaesthetic agent or a combination of hypnotic and analgesic agents. There has been no study to differentiate the analgesic potency from hypnotic potency of inhalation anaesthetics, because there is no way of differentiating both properties in the anaesthetic concentration range. Although some anaesthetic agents have been demonstrated to cause an increase in pain threshold in subanaesthetic concentrations [1–3], there has been no report that simultaneously evaluated both analgesic and hypnotic actions of inhalation anaesthetics. Therefore, we studied six currently available inhalation anaesthetics at subanaesthetic concentrations in terms of their effects on pain threshold and psychomotor function in normal volunteers.

METHODS AND RESULTS
The study was approved by the Medical Ethics Committee of Osaka University Medical School.
We studied six healthy male volunteers (mean age 37.4 yr, range 29–51 yr; weights 68.3 (SD 13.7) kg) after obtaining informed consent. Each subject was exposed to 100% oxygen and six inhalation anaesthetics at 7-day intervals. The subjects lay comfortably in a supine position for at least 10 min before measurements were made. The anaesthetic gases and oxygen were delivered via an anaesthetic circuit and face mask. End-tidal concentrations of anaesthetics and carbon dioxide were monitored using a Capnomac (Datex). The assessments of analgesic and hypnotic effects were undertaken using 20 trials of the psychomotor test, 25 trials of the pain threshold test and then 20 trials of the psychomotor test. Control, baseline measurements were made while the subject was breathing air via an anaesthetic circuit. After 10 min, one of the following anaesthetics diluted in oxygen 8–10 litre min"1 was administered to the subject: methoxyflurane, halothane, isoflurane, enflurane, nitrous oxide. The end-tidal concentration of each anaesthetic was adjusted to 0.2 MAC equivalent. After the end-tidal concentration was maintained at this value for 20 min, measurements were repeated at the same anaesthetic concentration. Seven series of experiments were performed in random order in a single subject with the six different anaesthetics, plus a control experiment using 100% oxygen.
Pain threshold was assessed using an improved radiant heat algometer (Nakahama Pain Meter NYT-55 (Kudo Electric)) [4]. The thermal output of the algometer was stabilized at a precision of ±1% using a power feedback mechanism. The surface temperature at the site of measurement was maintained constant at 36.5 °C. Five circular sticky tapes

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ANALGESIC AND HYPNOTIC EFFECTS OF INHALATION ANAESTHETICS

100% Oxygen  Methoxyflurane  Halothane  Isoflurane  Enflurane  Sevoflurane  Nitrous oxide

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Pain threshold (meals $^{1}$ cm$^{-2}$)

**P < 0.01 compared with 100% oxygen, halothane, isoflurane, enflurane and sevoflurane.  *P < 0.05 compared with 100% oxygen and halothane.**

Response time (ms)

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**P < 0.01 compared with 100% oxygen, halothane, isoflurane, enflurane and sevoflurane.  *P < 0.05 compared with methoxyflurane, halothane, sevoflurane and nitrous oxide.**

FIG. 1. Differences between values of pain threshold (A) and response time to auditory stimuli (B) measured while the subject breathed air or inhaled oxygen or anaesthetic gases at 0.2 MAC equivalent ($n=6$) (mean, SE). A:  **P < 0.01 compared with 100% oxygen, halothane, isoflurane, enflurane and sevoflurane.  *P < 0.05 compared with 100% oxygen and halothane.**  B:  **P < 0.01, ***P < 0.001 compared with 100% oxygen;  +P < 0.05 compared with methoxyflurane, halothane, sevoflurane and nitrous oxide.**

FIG. 2. Mean (±SE) residual effects of nitrous oxide on pain threshold and response time ($n=6$): changes from value before inhalation (B). D = During inhalation; A = 30 min after discontinuation of 100% oxygen (O) or 21% nitrous oxide (●).  *P < 0.05;  **P < 0.01 compared with 100% oxygen.

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Since the earliest study by Dundee and Moore [1], there have been several studies on analgesic actions painted black on each side and 18 mm in diameter were stuck to the proximal region of the forearm skin surface. These black spots were subjected, in order, to thermal stimulation by the metal plate of a stimulation head. Pain threshold was determined from the response to thermal stimuli of 3 s duration using the "up-and-down" method [5]: the first stimulus carried a thermal energy of 300 mcal s$^{-1}$ cm$^{-2}$; the thermal energy was increased if the stimulus did not cause pain, or decreased after pain. Heat energy was increased or decreased in 20-mcal steps until the sixth exposure, and in 10-mcal steps from the seventh. Heat stimuli were given 25 times at 40-s intervals.

The time elapsed from an auditory stimulus to striking the space key of a personal computer (Nihon Electric Company Ltd, PC 9801 VX) was defined as the response time. The auditory signal was generated by the computer in a random fashion. The frequency of the signal sound used was 1000 Hz and the intervals between sounds varied in the range 1–10 s. Measurements were made 20 times before and 20 times after the pain threshold test. The average value of 40 trails was taken as the response time.

When a subject was given nitrous oxide, additional measurements were performed 30 min after discontinuation of nitrous oxide in oxygen in order to examine any residual effects of the agent.

For statistical analysis, one-way analysis of variance with repeated measures, Dunnett's T test and Tukey's Studentized Range test were used.  $P < 0.05$ was considered significant.

Pain thresholds after methoxyflurane and nitrous oxide were significantly greater than in the control group (100% oxygen) (16.3 (23.8) mcal s$^{-1}$ cm$^{-2}$ ($P < 0.05$) and 44.2 (27.9) mcal s$^{-1}$ cm$^{-2}$ ($P < 0.01$), respectively) (fig. 1A). With the other anaesthetics, pain thresholds did not differ significantly from that in the control group. The pain threshold with nitrous oxide was significantly greater than those with all other anaesthetics tested ($P < 0.01$), with the exception of methoxyflurane. The pain threshold with methoxyflurane was significantly greater than with halothane group ($P < 0.01$).

The response time was increased with all anaesthetics compared with oxygen ($P < 0.01$) (fig. 1B). It was significantly longer with enflurane than with any other anaesthetic, with the exception of isoflurane. Both with enflurane and isoflurane, the subjects felt sleepy and three of the subjects intermittently fell asleep.

When tested 30 min after discontinuation of nitrous oxide, the pain threshold remained increased (24.6 (10.7) mcal s$^{-1}$ cm$^{-2}$, compared with 6.4 (11.8) mcal s$^{-1}$ cm$^{-2}$ with oxygen ($P < 0.05$)) (fig. 2). In contrast, psychomotor reaction time returned to the air-breathing value 30 min after discontinuation of nitrous oxide. There was no significant difference in response time between nitrous oxide (7.6 (13.6) s) and oxygen (3.1 (9.6) s) at this time (fig. 2).

COMMENT

Since the earliest study by Dundee and Moore [1], there have been several studies on analgesic actions...
of anaesthetic agents. Our data on nitrous oxide correspond well with results reported previously, but our data for methoxyflurane and halothane do not [1–3]. This is the first report on sevoflurane which suggests a lack of analgesic effect.

We found no differences in psychomotor response times when we compared anaesthetic agents with (methoxyflurane and nitrous oxide) and without (halothane and sevoflurane) analgesic property. We also found that enflurane reduced significantly greater response times than halothane or sevoflurane. These data suggest that hypnotic and analgesic properties are MAC determinants, but that the dose–effect relationship is strictly non-linear in terms of hypnotic or analgesic properties, and as a consequence, hypnotic and analgesic data determined, at sub-anaesthetic concentrations of inhalation anaesthetics cannot be extrapolated to MAC values.

We have shown that the analgesic action of nitrous oxide persists after its elimination from the body. This indicates that some analgesic substances may be produced by nitrous oxide in vivo. Berkowitz, Ngai and Finck [6] demonstrated that nitrous oxide produced dose-related analgesia and that opioid antagonists reduced its analgesic action in mice. They speculated that nitrous oxide could release endorphins or activate endorphin systems in the central nervous system.

Our data showing no residual effect of nitrous oxide on psychomotor response confirm the results reported by Korttila and colleagues [7], who also found no evidence of tolerance developing to the psychomotor effects of nitrous oxide.

REFERENCES