Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide

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Summary
The purpose of this study was to examine the effects of xenon and nitrous oxide in equipotent doses of 0.3 MAC on pain threshold and auditory response time in six healthy male volunteers. Compared with 100% oxygen inhalation, xenon and nitrous oxide significantly increased the pain threshold as measured by a radiant heat algometer. There was no significant difference in analgesic effects between xenon and nitrous oxide. Xenon significantly prolonged the response time to auditory stimuli compared with 100% oxygen, but nitrous oxide did not. The inhibitory effect of xenon on the auditory response time was significantly greater than that of nitrous oxide. The same six volunteers were studied to test if naloxone antagonized analgesia induced by xenon or nitrous oxide. The analgesic effects of xenon and nitrous oxide did not differ with or without naloxone. (Br. J. Anaesth. 1995; 74: 670-673)

Key words

Inert gases such as argon, krypton and xenon, which can form crystalline hydrates, have been reported to exert anaesthetic actions [1]. Since the efficacy of xenon as an anaesthetic for humans was established and reported by Cullen and Gross [2] in 1951, many studies have examined the anaesthetic properties of xenon. Xenon possesses advantages over nitrous oxide; it probably does not undergo biotransformation and is non-toxic [3]. Xenon is a more potent anaesthetic agent than nitrous oxide [4, 5]. Cullen and colleagues [4] reported that the MAC value for xenon is 71% in humans. It provides rapid induction and recovery from anaesthesia [5], it is expensive but costs may be minimized by using a minimum fresh gas flow in a circle system. Luttropp and colleagues [6] reported that xenon expenditure during 2 h of xenon anaesthesia via a fully automated minimal flow system was 7.6 litre in pigs weighing 37-39 kg.

Nitrous oxide produces good analgesia [7-9], but the analgesic properties of xenon have not been fully investigated. Therefore, we examined the analgesic and hypnotic effects of xenon at subanaesthetic concentrations and compared them with those of nitrous oxide in normal volunteers.

Subjects and methods
The study was approved by the Medical Ethics Committee of Osaka University Medical School and we obtained informed, written consent from each volunteer who was studied in two separate experiments.

COMPARATIVE STUDY OF ANALGESIC AND HYPNOTIC ACTIONS BETWEEN XENON AND NITROUS OXIDE
We studied six healthy male volunteers (mean age 22.3 (range 22-23) yr; weight 69.2 (SD 8.9) kg). The subjects were instructed not to take any beverages with stimulant or depressant actions from the previous night. Each subject was exposed to 100% oxygen, xenon or nitrous oxide at 7-day intervals. The order of exposure to these gases was varied randomly between volunteers. The anaesthetic gases and oxygen were delivered via an anaesthetic system and face mask. To ensure double-blinding, the gases were administered by staff other than those responsible for subject treatment and data collection. End-tidal concentrations of oxygen, carbon dioxide and nitrous oxide were monitored using a Capnomac (Datex), and xenon was monitored using a ThermoMat (Fuji Electric), which is a thermal conductivity gas monitor with a precision of ±1%.

We assessed analgesic effects by a pain threshold test and hypnotic effects by response times. Pain threshold was measured using an improved radiant heat algometer (Nakahama Pain Meter NYT-55, Kudo Electric) [9, 10] and determined as ascending and descending thresholds from the responses to thermal stimuli of 3 s duration [11]. Heat stimuli were given 25 times at 40-s intervals to five areas on the proximal region of the right forearm skin surface.

The interval between an auditory stimulus and the subject striking the space key of a personal computer (PC 9801 VX, Nihon Electric) was denned as the response time [9]. Twenty auditory signals generated by the computer were given in random order. Measurements were made twice before and after the pain threshold test. The average value of 40 trials was taken as the response time.

The subjects lay comfortably in a supine position...
for at least 10 min before measurements were made. The subject was then attached to the face mask and anaesthetic circuit. The first measurements (point 1; P1) were made while the subject was breathing air via a semi-closed system. Ten minutes after these measurements, the second set of measurements (point 2; P2) was made while the subject was breathing 100% oxygen via a semi-closed system. The subject then breathed air again. After 30 min the third set of measurements (point 3; P3) was made with air. Thereafter, xenon or nitrous oxide in oxygen 8 litre min
was given and subsequently the fresh gas flow was adjusted to maintain an end-tidal anaesthetic concentration equivalent to 0.3 MAC: 21% xenon or 30% nitrous oxide. After the end-tidal concentration was maintained at this value for 20 min, the fourth set of measurements (point 4; P4) was made at the same anaesthetic concentration. Control measurements were made while the subject was breathing 100% oxygen via a closed system.

Both pain thresholds and auditory response times were analysed in terms of the difference between the values of P1 and P2 and the difference between the values of P3 and P4 for each trial.

NALOXONE ANTAGONISM OF ANALGESIC ACTION

The same six male volunteers participated in this second experiment. Each subject was exposed twice to 100% oxygen, xenon or nitrous oxide at 7-day intervals. Both the order of exposure to oxygen, xenon or nitrous oxide and the administration of naloxone or saline were randomized. To ensure double-blindness, the anaesthetic gases and naloxone were administered by staff other than those responsible for subject treatment and data collection. The measurement of pain threshold was made by the same technique as that used in experiment 1. The first (baseline) measurement of pain threshold was made while the subject was breathing air via a semi-closed system. Ten minutes after baseline measurements, 100% oxygen (control), xenon or nitrous oxide (0.3 MAC equivalent) was inhaled via a closed system. After equilibration for 20 min, naloxone 0.01 mg kg
-1 or normal saline solution in the same volume was administered i.v. The second measurement was commenced 5 min after administration and repeated at the same anaesthetic concentration. Pain threshold was assessed in terms of the difference between the first and second measurements with or without naloxone.

Values are expressed as mean (SD). Pain thresholds and response times were compared using two-way analysis of variance (ANOVA) and post hoc testing was assessed using Tukey's test. The effect of naloxone was assessed using Student's paired t test. Significance was accepted as \( P < 0.05 \).

Results

COMPARATIVE STUDY OF ANALGESIC AND HYPNOTIC ACTIONS BETWEEN XENON AND NITROUS OXIDE

The differences between pain thresholds at P1 (first air) and P2 (100% oxygen) and those between P3 (second air) and P4 (agent) are shown in figure 1.

Figure 1. Differences in thermal pain thresholds between P1 (first air) and P2 (100% oxygen) and between P3 (second air) and P4 (agent) in control (■), nitrous oxide (□) and xenon (○) trials (n = 6) (mean, SE). P1–P4 are the same as in figure 1. * \( P < 0.05 \), ** \( P < 0.01 \) compared with control.

The pain threshold differences between P1 and P2 did not differ significantly between the three gas trials (ANOVA \( F \) ratio = 0.20, degrees of freedom (df) = 2, \( P = 0.825 \)). The pain threshold differences between P3 and P4 differed significantly between the three gas trials (ANOVA \( F \) ratio = 8.37, df = 2, \( P = 0.007 \)). The pain threshold differences with xenon and nitrous oxide (32.7 (14.2) mcal s
-1 cm
-2 and 26.2 (11.5) mcal s
-1 cm
-2, respectively) were significantly greater than those (5.7 (8.7) mcal s
-1 cm
-2) with the control (100% oxygen) (\( P < 0.01 \) and \( P < 0.05 \), respectively). There was no significant difference in pain threshold between xenon and nitrous oxide.

Differences in the response times to auditory stimuli between P1 (first air) and P2 (100% oxygen) and between P3 (second air) and P4 (agent) in control (■), nitrous oxide (□) and xenon (○) trials (n = 6) (mean, SE). P1–P4 are the same as in figure 1. * \( P < 0.05 \) compared with nitrous oxide or control.

The response time differences between P1 and P2 did not differ significantly between the three gas trials (ANOVA \( F \) ratio = 3.22, df = 2, \( P = 0.083 \)) (fig. 2). The response time differences between P3 and P4 differed significantly (ANOVA \( F \) ratio = 6.38, df = 2, \( P = 0.016 \)). The response time difference between P3 and P4 with xenon (98.7 (81.6) ms) was significantly greater than those with 100% oxygen (1.8 (23.2) ms) and nitrous
Curves for nitrous oxide and xenon may differ [12].

Defining only one point on a dose-response curve, the xenon than nitrous oxide at 0.3 MAC. As MAC analgesia and hypnosis may be more potent with data indicate that anaesthetic actions comprising 0.3 MAC. These data suggest that xenon has a more potent analgesic effect than methoxyflurane.

In the present study we found that the clinical dose of naloxone did not antagonize the analgesic actions of either nitrous oxide or xenon. This suggests that the endorphin system may not be involved in analgesia induced by these two gases. The dose of naloxone used in this study may not have been adequate to fully antagonize the opioid effects [21], but it was not too small to produce clinical reversal [22]. As large doses of naloxone were used in those studies which observed reversal effects, it is possible that these effects might not be related to the opioid system but to direct effects. Thus analgesia induced by xenon and nitrous oxide may result from non-opioid actions.

**Discussion**

We have previously studied the analgesic effects of nitrous oxide and five volatile anaesthetics: methoxyflurane, halothane, enfurane, isoflurane and sevo-flurane, at subanaesthetic concentrations of 0.2 MAC, and showed that only nitrous oxide and methoxyflurane possessed analgesic effects [9] and nitrous oxide was more potent. In the present study we observed that xenon had an analgesic action similar to that of nitrous oxide in equipotent doses of 0.3 MAC. These data suggest that xenon has a more potent analgesic effect than methoxyflurane.

We also found that xenon prolonged the response time significantly more than nitrous oxide at the same anaesthetic concentration of 0.3 MAC. These data indicate that anaesthetic actions comprising analgesia and hypnosis may be more potent with xenon than nitrous oxide at 0.3 MAC. As MAC defines only one point on a dose–response curve, the curves for nitrous oxide and xenon may differ [12].

**References**

2. Cullen SC, Gross EG. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. Science 1951; 113: 580-582.
9. Tomi K, Masmoto T, Tashiro C, Yagi M, Pak M, Nishimura...
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