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Comparison of the analgesic potency of xenon and nitrous oxide in humans evaluated by experimental pain

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Summary

We have compared the analgesic potency of MAC-equivalent concentrations of xenon (10, 20, 30 and 40%) and nitrous oxide (15, 30, 45 and 60%) in humans using a multimodal experimental pain testing and assessment technique. We tested 12 healthy volunteers in a randomized, single-blind, crossover study. The following experimental pain tests were used: nociceptive reflex to repeated stimuli; pain tolerance to maximal effort tourniquet ischaemia; electrical stimulation; mechanical pressure; and cold. Reaction time was also measured. Xenon and nitrous oxide produced analgesia to ischaemic, electrical and mechanical stimulation, but not to cold pain. There was no difference in MAC-equivalent concentrations of xenon and nitrous oxide. Both increased reaction time in a similar manner. Xenon and nitrous oxide evoked nausea and vomiting in a large number of volunteers (*Br. J. Anaesth*. 1998; **81**: 742–747).

Keywords: anaesthetics gases, nitrous oxide; anaesthetics gases, xenon; pain, experimental

The anaesthetic properties of xenon in humans were first reported by Cullen and Gross in 1951.[1] Xenon possibly has a future as an anaesthetic, replacing nitrous oxide.[2] In contrast with nitrous oxide, xenon is non-toxic and probably metabolically inert. Nitrous oxide can be a health hazard after prolonged exposure to low concentrations.[3–5] Nitrous oxide is teratogenic in rats, whereas xenon is not.[6] Also, xenon is harmless to the ozone layer and probably more potent than nitrous oxide.[7 8] The main limiting factor for the widespread use of xenon has been its very high cost. However, costs can be reduced using anaesthetic machines with recycling systems for xenon.

A recent study[9] showed no statistically significant difference in the analgesic effects of 0.3 MAC of xenon (21%) and nitrous oxide (30%).[10 11] However, only a small number of volunteers were studied ($n=6$) and only pain thresholds to heat stimulations were measured. Utsumi and colleagues[12] found that 70% xenon and 70% nitrous oxide suppressed spinal cord dorsal horn neurones to a similar degree, with no significant difference between the two agents.

The importance of using a multimodal testing and assessment technique can be demonstrated by the following example. Propofol in subanaesthetic concentrations increases the threshold of the nociceptive reflex to single stimulations.[13] If we compare this result with earlier studies with different analgesic drugs using the same stimulation methodology,[14–20] we could conclude that propofol has an analgesic effect. But propofol does not affect the threshold of the nociceptive reflex to repeated stimulations,[13] which would indicate that propofol, after repeated stimulations, does not have an analgesic effect. However, propofol reduces pain tolerance to mechanical pressure, indicating a hyperalgesic effect on mechanical pressure.[13]

The aim of our study was to use a multimodal experimental pain testing and assessment technique to compare the analgesic potency of xenon and nitrous oxide in humans.

Subjects and methods

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Bern, and written informed consent according to the Helsinki Declaration was obtained. We studied 12 healthy volunteers (median age 24.0 (range 22–30 yr)), who were not receiving any medications, had no allergies or previous adverse reactions to anaesthesia in a randomized, single-blind, crossover study. Female volunteers were excluded if they were pregnant. They were investigated on two different days with at least a 48-h interval. Because of logistical reasons (separate anaesthetic machines and gas analysers for xenon and nitrous oxide), volunteers could not be blinded to the person carrying out the tests, but were blinded to the gas used.

To minimize the risk of acid aspiration, volunteers were tested after a fasting period of at least 6 h, and before testing they received ranitidine 150 mg dissolved in water. During testing, volunteers rested comfortably in the supine position. An i.v. infusion of saline was started and haemoglobin oxygen saturation by pulse oximetry, ECG and non-invasive arterial pressure were monitored continuously during the experiment. Subanaesthetic gas concentrations were delivered via a face mask fastened with conventional

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rubber straps. Inspiratory and expiratory gases were sampled close to the nostrils via a plastic tube fitted through a hole drilled in the mask. Inspired and end-tidal nitrous oxide, oxygen and carbon dioxide concentrations were analysed using a Capnomac Ultima (Datex, Helsinki, Finland) and stored on a personal computer. Inspired xenon was analysed using a mass spectrometer (Xenotec 2000, Leybold, Köln, Germany). The gas monitors were calibrated before each investigation. The following experimental tests were applied in the order listed below.

NOCICEPTIVE REFLEX TO REPEATED STIMULI

The sural nerve was stimulated behind the right lateral malleolus via surface electrodes filled with electrode gel (inter-electrode distance approximately 3 cm). A 25-ms stimulus (in reality a train-of-five 1-ms square wave impulses, which is perceived as a single stimulus) was repeated five times with a frequency of 2 Hz.[21] Electromyographic (EMG) reflex responses were recorded with surface electrodes placed over the middle of the biceps femoris and rectus femoris. Current intensity was increased from 1–2 mA in steps of 1–2 mA until summation in the reflex response was observed. Summation was defined as an increase in amplitude of the fourth and/or fifth reflexes of at least 50% compared with the first and/or second reflexes.[20 22 23] The summation threshold was defined as the minimal current intensity that could repeatedly elicit a summation response in the EMG.

ISCHAEMIC PAIN TOLERANCE

Pain tolerance to maximal effort tourniquet ischaemia was used.[24] An arterial pressure cuff was placed on the right arm. The volunteer exercised at maximal effort with a calibrated handgrip trainer at a strength of 25 pounds for 2 min. The cuff was then immediately inflated and the pressure kept constant at 250 mm Hg for a maximum of 2 min. If pain was considered intolerable before 2 min had elapsed, the volunteer could verbally indicate this. The elapsed time was noted, and the cuff was deflated. Perceived pain intensity was rated continuously using an electronic visual analogue scale (VAS) and recorded on a personal computer. Duration of ischaemia, peak pain and area under the pain intensity–time curve were determined. If the cuff was deflated before the end of 2 min, pain intensity was considered to be maximal until the end of the period (for calculation of area under the curve).

ELECTRICAL PAIN TOLERANCE

A 1-mm diameter intracutaneous electrode[25] was applied to the second toe of the left foot. Intracutaneous placement was accepted if the sensory threshold was less than 0.5 mA. Electrical pain tolerance thresholds were determined with a 25-Hz train of 0.5-ms constant-current square wave pulses of increasing intensity (0.01 mA per stimulation, maximum intensity 10 mA) delivered from a computer-controlled stimulator (University of Aalborg, Denmark). The volunteer was instructed to press a button when the pain became intolerable. The current intensity at this point was recorded and defined as the electrical pain tolerance threshold. Four stimulations were given (inter-stimulus interval 10–20 s) and the average of the last three determinations was calculated.

PRESSURE PAIN TOLERANCE

Pressure pain tolerance thresholds were determined on the centre of the pulp of the second and third finger of the left hand with an electronic pressure algometer (Somedic AB, Stockholm, Sweden).[20 22 26–29] A probe with a surface area of 0.28 cm^2 was used, and the pressure increase was set to 30 kPa s^{-1}. Pain tolerance was defined as the point when the volunteer did not want the pressure to be increased further. For determination of the threshold, the mean of two consecutive measurements was used.

COLD PAIN TOLERANCE

A 2-min ice water test was used.[20 22 30 31] Before immersion, the skin temperature on the thenar of the left hand was measured and if it was less than 30.0 °C, the hand was warmed until skin temperature was more than 30.0 °C. The left hand was then immersed in ice saturated water (1.5 ± 1.0 °C) which was stirred continuously during immersion. If pain was considered intolerable before 2 min had elapsed, the volunteer could withdraw the hand, and the elapsed time was noted. Perceived pain intensity was rated continuously with an electronic visual analogue scale (VAS) and recorded on a personal computer. Duration of immersion, peak pain and area under the pain intensity–time curve were determined. If the hand was withdrawn before the end of 2 min, pain intensity was considered to be maximal until the end of the 2-min period (for calculation of area under the curve).

REACTION TIME

A 1000-Hz tone was delivered from a computer with randomized intervals of 3–8 s, and a timer started simultaneously. The volunteer was told to press a button as fast as possible after each tone. Reaction time was defined as the time from the tone until the volunteer pressed the button. The mean of five consecutive measurements was used.

The pain tests were explained to the volunteer and a trial testing of all techniques was performed in order to familiarize the volunteer with the procedure. The mask was then fitted until the volunteer felt comfortable, and there were no leaks. Thereafter the volunteer breathed oxygen for a minimum of 5 min via a semi-closed breathing system (Cicero EM Xenon, Dräger, Lübeck, Germany).

PROCEDURE

A baseline test series of the above tests was performed. Thereafter, according to the randomization, xenon or nitrous oxide in MAC-equivalent concentrations[10 11] was introduced slowly into the breathing system (fresh gas flow 3 litre min^{-1}) and adjusted to the first concentration. For xenon, volunteers received 10, 20, 30 and 40% (inspired), and for nitrous oxide 15, 30, 45 and 60% (end-tidal). We had

planned to randomize whether the gases should be given in an ascending or descending order, but one of the authors in a pilot study vomited within 5 min after receiving 50% nitrous oxide, and the first volunteer given nitrous oxide in a descending series also vomited after receiving 60% which prevented completion of the experiment. Thereafter, all gas concentrations were given in ascending order.

Testing was started after a 10-min equilibration period at constant inspired (xenon) or end-tidal (nitrous oxide) concentrations. After testing had been performed at all four concentrations, the gas was discontinued. A final post-gas test series was performed after the volunteer had breathed oxygen via the mask for 30 min. At the two lowest concentrations of xenon and nitrous oxide and at the post-gas test series, all experimental tests were performed (duration of test series 15–18 min). At the two highest concentrations of xenon and nitrous oxide, ischaemic pain and cold pain tolerance were not determined, as these require a higher degree of co-operation than pressing a button when the pain becomes intolerable (duration of test series 5–8 min). The inspired to end-tidal nitrous oxide concentration difference during the last 5 min of each equilibration period was later calculated from the stored data.

Statistical analysis was performed independently for each pain test. The numerical values for each measurement were transformed to percentage of baseline measurements. To determine if there was a statistically significant trend over concentrations, the Page test for ordered alternatives was used for each pain test and gas. For each pain test, the assumed equi-effective concentrations of xenon and nitrous oxide were compared using the Wilcoxon signed ranks matched pairs test. The Wilcoxon test was also used to test for an effect of time on each pain test by comparing baseline with post-gas measurements for each gas. $P<0.05$ was considered significant.

Results

For the two lowest concentrations of xenon (10 and 20%) and nitrous oxide (15 and 30%), testing was performed in 11 of the 12 volunteers. One volunteer developed myoclonia-like side effects after administration of 20% xenon, and further administration of xenon was stopped. Because of nausea and vomiting, testing was only possible in a few volunteers at 45% xenon and 60% nitrous oxide, and therefore statistical analysis could not be performed at the highest concentration. For the nociceptive reflex to repeated stimulations, statistical analysis was performed at the three remaining concentrations; for all other tests, analysis was performed at the two lowest gas concentrations. Figure 1 summarizes the results for 20% xenon and 30% nitrous oxide.

The nociceptive reflex to repeated stimuli was tested in eight volunteers at three concentrations of xenon (10, 20, 30%) and three concentrations of nitrous oxide (15, 30, 45%) (table 1). There was a significant trend for an increase in the threshold to nociceptive reflex to repeated stimulations for increasing concentrations of both xenon ($P<0.001$) and nitrous oxide ($P<0.001$). There was no significant difference between MAC-equivalent concentrations of xenon and nitrous oxide.

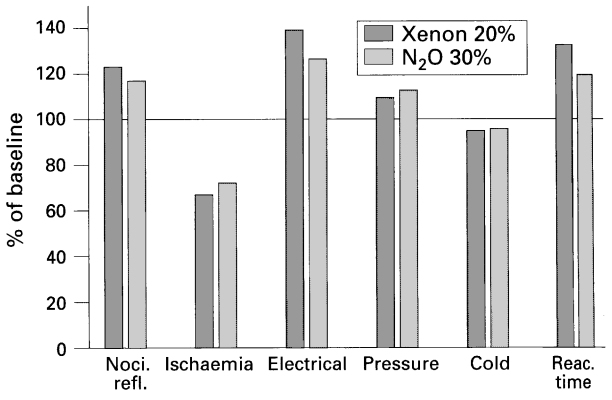

Figure 1 Effects of 20% xenon and 30% nitrous oxide (N_2O) on the nociceptive reflex (Noci. refl.), ischaemic pain tolerance (area under the pain intensity–time curve), electrical pain, pressure pain tolerance, cold pain tolerance (area under the pain intensity–time curve) and reaction time. Results are expressed as percentage of baseline values.

For increasing concentrations of both xenon and nitrous oxide, there was a significant trend in (table 2): (1) reduction in the area under the pain intensity–time curve for ischaemia (xenon $P<0.001$, nitrous oxide $P<0.001$) but not for cold; (2) reduction of the maximal or peak pain intensity for ischaemia (xenon $P<0.05$, nitrous oxide $P<0.01$) but not for cold; (3) increase in duration of cold (xenon $P<0.05$, nitrous oxide $P<0.01$) but not ischaemic pain; (4) increase in electrical (xenon $P<0.001$, nitrous oxide $P<0.01$) and mechanical pressure (xenon $P<0.01$, nitrous oxide $P<0.001$) pain tolerance; and (5) increase in reaction time (xenon $P<0.001$, nitrous oxide $P<0.001$).

There was a significant difference between the reduction in the area under the ischaemic pain intensity–time curve for 10% xenon and 15% nitrous oxide ($P<0.05$) and in the difference between the increase in electrical pain tolerance for 10% xenon and 15% nitrous oxide ($P<0.05$), and for 20% xenon and 30% nitrous oxide ($P<0.02$).

Except for sensory threshold ($P<0.05$) and pain tolerance ($P<0.05$) to electrical stimulation, and duration of immersion in iced water for nitrous oxide ($P<0.02$), there was no effect of time (post-gas values were not significantly different from baseline) on the pain tests (table 3).

The inspired to end-tidal nitrous oxide concentration difference during the last 5 min of each equilibration period was not more than 1%.

Of the 11 volunteers tested with both xenon and nitrous oxide, nine experienced nausea at 30% xenon and seven at 45% nitrous oxide. Vomiting occurred in six volunteers after 30% xenon and in six after 45% nitrous oxide.

Discussion

Our study showed that xenon and nitrous oxide attenuated pain induced with different modalities in a similar manner, indicating that they have similar analgesic profiles. The analgesic potency of xenon was approximately 1.5 times higher than that of nitrous oxide. Both xenon and nitrous oxide evoked nausea and vomiting in a large number of volunteers.

The MAC values of xenon and nitrous oxide have

Table 1 Numerical results for the nociceptive reflex to repeated stimulations. All values are median (25–75 percentiles), and are expressed as percentage of baseline values (baseline = 100%). There was a significant trend for increasing concentrations of both xenon and nitrous oxide

Xenon		Nitrous oxide	
Concentration	% of baseline	Concentration	% of baseline
10%	114.3 (100.0–120.0)	15%	100.0 (100.0–121.7)
20%	122.5 (100.0–130.8)	30%	116.7 (102.5–126.4)
30%	150.0 (100.0–164.2)	45%	140.0 (115.7–152.9)

Table 2 Numerical results for the experimental pain tests and reaction time. All values are median (25–75 percentiles), and are expressed as percentage of baseline values (baseline = 100%). $\star P < 0.05$ for a significant trend for increasing concentrations of both anaesthetics

	Xenon		Nitrous oxide	
Test	10%	20%	15%	30%
Ischaemic pain tolerance–peak pain$\star$	93.3 (52.9–100.0)	93.4 (50.0–100.0)	100.0 (77.6–100.0)	79.8 (36.9–97.4)
Ischaemic pain tolerance–AUC$\star$	72.5 (42.4–94.8)	67.1 (55.7–73.7)	94.7 (82.1–98.8)	71.9 (30.9–87.4)
Electrical–pain tolerance$\star$	130.6 (111.0–146.5)	138.7 (122.5–219.0)	112.6 (102.1–117.20)	126.2 (112.1–171.9)
Mechanical pressure–pain tolerance$\star$	106.8 (105.6–111.7)	109.7 (103.1–122.1)	105.4 (101.1–109.4)	112.4 (106.1–116.4)
Cold pain tolerance–duration of immersion$\star$	112.5 (103.0–126.5)	119.6 (100.0–148.5)	106.6 (100.0–112.5)	121.0 (100.0–158.5)
Cold pain tolerance–peak pain	100.0 (100.0–100.0)	100.0 (94.7–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)
Cold pain tolerance–AUC	98.6 (91.2–101.6)	94.8 (84.3–98.6)	99.5 (98.0–103.9)	95.7 (93.9–97.6)
Reaction time$\star$	106.3 (87.4–131.3)	132.5 (123.2–143.8)	100.0 (92.4–116.7)	119.8 (109.5–178.2)

Table 3 Effect of time on the pain test was assessed by comparing post-gas values with baseline. All values are median (25–75 percentiles), and are expressed as percentage of baseline values (baseline = 100%). $\star P < 0.05$

Test	Xenon	Nitrous oxide
Temporal summation	100.0 (100.0–125.0)	113.9 (100.0–120.0)
Ischaemic pain tolerance–duration	100.0 (100.0–100.0)	100.0 (100.0–111.9)
Ischaemic pain tolerance–peak pain	100.0 (90.8–100.0)	100.0 (76.6–100.0)
Ischaemic pain tolerance–AUC	96.4 (90.1–102.4)	95.5 (82.6–104.1)
Electrical–pain tolerance	112.5 (86.1–126.4)	111.1 (100.0–138.6)$\star$
Electrical–pain sensory threshold	133.3 (100.0–150.0)	133.3 (100.0–162.5)$\star$
Mechanical pressure–pain tolerance	99.3 (86.7–105.9)	97.9 (92.5–102.9)
Cold pain tolerance–duration of immersion	81.8 (76.3–100.0)	91.9 (75.4–100.0)$\star$
Cold pain tolerance–peak pain	100.0 (100.0–100.0)	100.0 (100.0–102.8)
Cold pain tolerance–AUC	104.4 (102.1–110.4)	103.2 (99.4–108.7)
Reaction time	100.0 (100.0–125.0)	113.9 (100.0–120.0)

been reported to be 70%[10] and 105%,[11] respectively. Xenon is therefore 1.5 times more effective in depressing gross purposeful movement to skin incision than nitrous oxide. In our study, 1.5 times greater concentrations of nitrous oxide were compared with xenon. In no test was nitrous oxide more effective than xenon, but xenon increased pain tolerance to electrical stimulation significantly more than MAC-equivalent doses of nitrous oxide. The significant difference between 10% xenon and 15% nitrous oxide for area under the pain intensity–time curve for ischaemic pain, and the slight decrease in duration of immersion in iced water at the post-gas measurement for nitrous oxide could be a result of chance, as the probability of a type I error increases with increasing number of comparisons between concentrations. The small but significant increase in electrical pain tolerance at the post-gas measurement was probably a result of a simultaneous increase in the sensory threshold. Cullen and Gross,[1] using heat pain thresholds, found a 15% increase in pain thresholds with both gases (50% xenon and 50% nitrous oxide). Yagi and colleagues[9] found no statistically significant difference in the analgesic effects of 0.3 MAC of xenon (21%) and nitrous oxide (30%). However, only a small number of volunteers were studied ($n = 6$), and only pain thresholds to heat stimulation were measured. In their study, 21% xenon increased the response time four times more than 30% nitrous oxide, indicating that the sedative–hypnotic potency of xenon is more than 1.5 times that of nitrous oxide. Our study supports this assumption, as we also found that 20% xenon increased reaction time (similar to the response time of Yagi and co-workers) more than 30% nitrous oxide. Utsumi and colleagues[12] found that 70% xenon and 70% nitrous oxide suppressed spinal cord dorsal horn neurones to a similar degree, indicating no statistically significant difference in the direct spinal effects of xenon and nitrous oxide.

For equilibration of nitrous oxide, end-tidal concentrations were used as these can be measured easily with conventional anaesthetic gas analysers. Xenon cannot be measured with conventional anaesthetic gas analysers. In our study, a mass spectrometer was used. As this was not prepared for breath-to-breath end-tidal measurements, we could only measure inspired concentrations of xenon. However, the blood-gas solubility of xenon is 0.14 compared with 0.47 for nitrous oxide. Therefore, because of the fast kinetics of xenon and a fresh gas flow of 3 litre min^{-1}, a 10-min equilibration period should ensure an end-tidal xenon concentration close to fresh gas concentrations. For nitrous oxide, the inspired to end-tidal concentration difference

during the last 5 min of each equilibration period was not more than 1%. The actual xenon concentrations might have been slightly lower than intended. This would further support the assumption that the analgesic potency of xenon is higher than 1.5 times that of nitrous oxide.

The high incidence of nausea and vomiting in our study with both xenon and nitrous oxide was surprising. After the first cases of nausea and vomiting, we learnt to recognize impending nausea and vomiting, and discontinued administration before nausea progressed to vomiting. The real incidence of vomiting could therefore be higher. Lorenz and colleagues[32] found no nausea with 33% xenon or Sclabassi and colleagues[33] with 25, 30 and 35% xenon. However, administration time was short in both studies. Several studies using up to 10 min administration of up to 50% nitrous oxide reported no nausea and vomiting.[34–36] Rupreht and colleagues[37] found a high incidence of nausea (six of eight volunteers) and vomiting (number not reported) in volunteers breathing 60–80% nitrous oxide for at least 45 min. In our volunteers, nausea quickly vanished after discontinuation of nitrous oxide or xenon. Nitrous oxide has been considered to contribute to postoperative nausea and vomiting,[38–42] as have inhalation anaesthetics and opioids.[38 39] Xenon would presumably also contribute to postoperative nausea and vomiting, but this has not been studied in depth. Xenon is a more potent analgesic than nitrous oxide and therefore the peroperative need for opioids is reduced.[7] Xenon might be a sufficiently potent hypnotic to allow omission of further inhalation agents. Therefore, the postoperative incidence of nausea and vomiting with xenon might be less than that with nitrous oxide.

Considering the beneficial effects of xenon on haemodynamic reactions[7 43 44] and catecholamine release,[7 44] and that the analgesic and probably the sedative–hypnotic potencies of xenon are at least 1.5 times higher than those of nitrous oxide, we believe that further investigations on xenon as an anaesthetic are warranted.

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