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Nitrous Oxide and Dysrhythmias

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Nitrous oxide is used routinely as an adjunct to anesthesia with enflurane, halothane, isoflurane, and narcotics. Although dysrhythmias often occur intraoperatively, they have not been attributed to N₂O, possibly because physicians are unaware such a relationship exists. This case report and subsequent documentation in five of nine additional patients demonstrates that administration of N₂O may be responsible for some episodes of atrioventricular junctional rhythm (AVJR).

REPORT OF A CASE

A 24-yr-old man (97 kg) was scheduled for bone graft for repair of nonunion of the right tibia. The patient had no other known medical problems. Preoperative arterial blood pressure was 122/82 mmHg, heart rate 80 beats/min, and respiratory rate 16 breaths/min. The patient was given 10 mg of diazepam po and 10 mg of morphine sulfate im 1½ h before arrival in the operating room. While breathing 100% oxygen, he was given 700 µg of fentanyl iv in divided doses, followed by 3 mg of *d*-tubocurarine, 300 mg of thiopental, and 120 mg of succinylcholine. After endotracheal intubation, an additional 1,800 µg of fentanyl iv were given. Controlled ventilation (with a tidal volume of 1,000 ml and a rate of 10 breaths/min) was instituted with 90% oxygen and 10% N₂O (ten percent N₂O was administered because it was erroneously thought to prevent diffusion atelectasis). Peak inspiratory pressure was 28 cm H₂O. Ninety minutes later, after a long period of stable vital signs, heart rate increased from 60 to 70 beats/min, and systolic blood pressure from 110 to 120 mmHg. Spontaneous movement of the head accompanied these changes. In response, we increased the concentration of N₂O from 10 to 70%. Within 3 min, systolic blood pressure decreased to 95 mmHg, heart rate decreased to 60 beats/min, and AVJR replaced normal sinus rhythm (NSR). Nitrous oxide was discontinued and 100% oxygen was administered. Three minutes later, NSR was reestablished, systolic blood pressure increased

to 110 mmHg, and heart rate to 70 beats/min. A 12-lead electrocardiogram (ECG) was attached to the patient; lead II was selected to best detect P waves. Six consecutive times, 100% oxygen was administered in place of 60 or 70% N₂O in oxygen when AVJR occurred. In all instances, NSR was reestablished approximately 3 min after discontinuation of N₂O (fig. 1). During these episodes, the heart rate ranged from 90–115 beats/min during sinus rhythm, to 80–118 beats/min during AVJR. During administration of 40% oxygen, PaO₂ was 230 mmHg, PaCO₂ was 42.7 mmHg, and pH_a was 7.42; peak inspiratory pressure was not affected by N₂O.

ADDITIONAL STUDIES

Since this initial case in 1981, we have examined the relationship between administration of N₂O and the occurrence of AVJR in nine additional patients. Data were collected only if the following conditions existed: a NSR

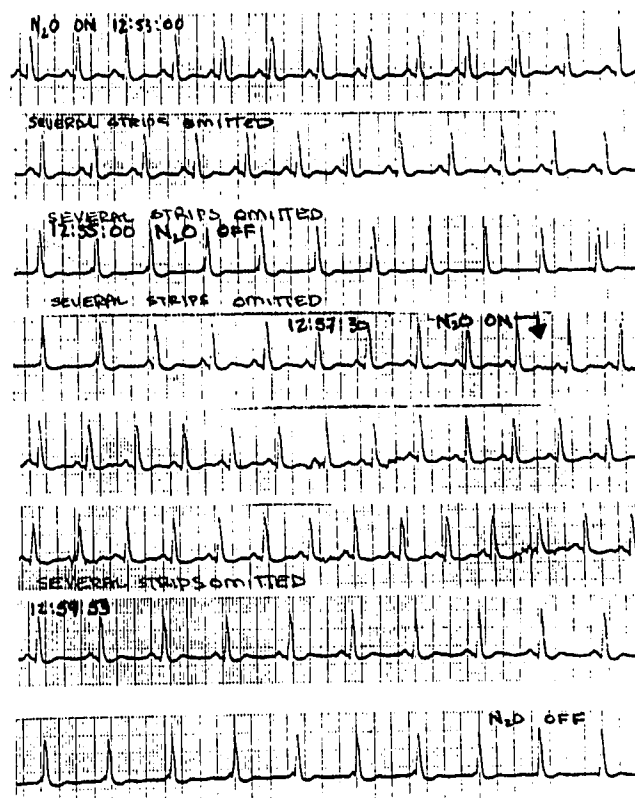


FIG. 1. Lead II electrocardiogram shows that administration of 70% N₂O caused sinus rhythm to become atrioventricular junctional rhythm. Administration of 100% O₂ led to resumption of sinus rhythm. Sequence recurred six times in the next 25 min. Paper speed was 25 mm/sec.

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8	F/55	10/22/82 Carotid Dilatation	None	Premed: Time: Rhythm: BP (mmHg): HR (bpm): E.T. N ₂ O (%): E.T. halothane (%):	None AJVR 86/50 110 60 0.56 None 0	AVJR did not return with 60% N ₂ O 4 min later NSR 99/50 100 0 0.82
9	F/40	Thyroidectomy for medullary carcinoma	Pheochromocytoma	Premed: Time: Rhythm: BP (mmHg): HR (bpm): E.T. N ₂ O (%): E.T. isoflurane (%):	AVJR 110/70 95 60 1.04 None 0 AVJR 94/63 68 40 1.44	5 min later AVJR 110/68 97 60 1.4
10	M/40	6/20/84 Lumbar laminectomy	None	Premed: Time: Rhythm: BP (mmHg): HR (bpm): E.T. N ₂ O (%): E.T. enflurane (%):	None 0 AVJR 85/59 69 15 1.57	2 min later NSR 110/68 96 0 1.32 3 min later NSR 85/59 69 15 1.57
						NSR did not return despite: 1) No N ₂ O 2) Varying concs. of isoflurane (0.85 to 1.54%) 3 min later NSR 105/76 63 20 1.01

AVJR = atrioventricular junctional rhythm; BP = blood pressure; E.T. = end-tidal concentration; HR = heart rate; Insp = inspired concentration; M.S. = morphine sulfate; ND = not done; NR = not recorded; NSR = normal sinus heart rhythm.

before induction of anesthesia; a period of "stable" surgical stimulation; a 5-min period of "stable" AVJR; and an end-tidal carbon dioxide tension (as determined by mass spectrometry) or a PaCO₂ of 35-45 mmHg. Also, patients had to be receiving anesthesia delivered from a machine that enabled nitrogen to be substituted for N₂O.

Before surgery, all patients gave informed consent to participate in data collection protocols approved by the UCSF Committee on Human Experimentation. In addition, each patient retroactively gave informed consent regarding disclosure of data in this report. Because of the infrequent occurrence of "stable" AVJR during anesthesia, the specific test we chose (*i.e.*, replacing N₂O with nitrogen) was not specifically approved by any patient. However, determining the cause of dysrhythmias was considered a part of clinical care.

After 5 min of AVJR, a lead II ECG was recorded continuously. Then nitrogen was substituted for N₂O. At the same time that nitrogen was substituted for N₂O, an attempt was made to keep anesthetic depth constant by increasing the amount of volatile anesthetic agent the patient received. Although we knew that keeping anesthetic depth constant would be difficult because of the different time courses of equilibration between brain tissue and alveolar gas partial pressures of anesthetics with different blood solubilities, we attempted to do so by greatly altering the inspired concentration of volatile agent at the same time that we changed the concentration of N₂O. We noted the time of the return of sinus rhythm, after which N₂O was substituted for nitrogen. We then noted the time of the return of AVJR. If surgical stimulation was still stable and time permitted, we repeated this procedure several times. In three patients, samples of blood for plasma catecholamine levels were drawn during the dysrhythmia and, after it subsided, to rule out the possibility that the patient had a disease causing sympathetic dysfunction.

RESULTS

In five of nine patients (patients 2, 3, 5, 6, and 10; table 1) AVJR converted to sinus rhythm each time nitrogen was substituted for N₂O, and sinus rhythm returned to AVJR every time N₂O was readministered. In patient 7, sinus rhythm did not return for over 30 min, at which time the patient was receiving 60% N₂O. In patient 8, after AVJR converted to sinus rhythm, AVJR did not recur during administration of N₂O. In patients 4 and 9, AVJR converted to sinus rhythm the first time nitrogen was substituted for N₂O and the volatile agent was increased, but did not do so the second time. In the three patients in whom they were measured, plasma catecholamine levels did not differ during AV junctional or sinus rhythm. During AVJR, norepinephrine was 247 ± 62 pg/ml, and epinephrine was 122 ± 48 pg/ml; during

NSR, norepinephrine was 258 ± 54 pg/ml, and epinephrine was 139 ± 50 .

DISCUSSION

The results of this study suggest that N_2O may be capable of provoking AVJR in humans. Although dysrhythmias may occur in over 60% of operative procedures,[§] in our experience, the occurrence of AVJR in a surgical patient rarely elicits the response of reducing the concentration of N_2O . Halothane and enflurane are known to affect conduction.^{1,2} However, when used with either halothane or enflurane, N_2O has never been implicated as the cause of AVJR. Yet, in six of our ten patients, each time N_2O was administered and the concentration of volatile agent decreased, AVJR occurred. The infrequent occurrence of a 5-min period of this dysrhythmia in patients who had given informed consent, and in whom we could readily substitute nitrogen, led us to choose a protocol proving N_2O to be the causative agent by trying to provoke the dysrhythmia after it had subsided. Rather than randomly switch or not switch patients to nitrogen from N_2O , we sought to determine the cause by discontinuing N_2O and then documenting recurrence upon reexposure. These measures were carried out in six of ten patients. Because it could be argued that AVJR might be caused by too great a dose of anesthesia or treated by increasing the depth of anesthesia, we tried to keep the total MAC equivalent of anesthesia constant, by substantially increasing the end-tidal concentration of volatile agent by the equivalent of 0.5 MAC in most cases (table 1). This method leaves doubt as to whether it was the discontinuation of N_2O , or the addition of more volatile agent that resulted in the return to NSR. This question did not arise in our index case, because the patient did not receive a volatile agent.

Atrioventricular junctional rhythm results from depression of sinus node activity or conduction to the AV node with subsequent escape rhythm from the AV junction, or from enhancement of AV junctional automaticity. In our initial patient and in patients 2, 3, 5, and 10, administration of N_2O was associated with an AVJR at a rate slower than the previous sinus rate. Presumably, either sinus node activity was suppressed, or conduction through the atrium or at the AV node was decreased. Possible mechanisms include a direct effect of N_2O on the sinoatrial (SA) node, intraatrial conduction, or the AV node. Other factors, such as delivery of electrolytes to pacemaker tissue in the SA node, increased vagal stimulation, or decreased sympathetic tone, also may have

contributed to the effects seen with N_2O . We tried to keep anesthetic levels constant: when we decreased the delivered concentration of N_2O , we increased the delivered concentrations of the other volatile anesthetics. However, the differing pharmacokinetic characteristics of the agents make it unlikely that we were successful in doing so (table 1). Thus, it is possible that N_2O decreased sympathetic stimulation and thereby fostered the development of AVJR. This explanation implies that extra sympathetic stimulation (*e.g.*, that caused by surgical pain) was required to sustain sinus node function, and this possibility is unlikely. In addition, reduction of sympathetic stimulation was not corroborated by analysis of plasma catecholamine levels in blood samples obtained during changes in heart rhythm. These levels did not differ during AV junctional or sinus rhythm in the three patients in whom they were measured (see "Results"). Admittedly, this indicator of sympathetic tone may not be sensitive to changes in sympathetic tone at any one receptor site, such as the SA or AV nodes. Furthermore, in patients with heart disease, who volunteered for the study, N_2O appears to cause minor but significant sympathetic stimulation.³⁻⁶

Because of the lack of dysrhythmias and the relative cardiovascular stability it confers, N_2O has been thought to be relatively safe. It has even been recommended to use 30–50% N_2O to treat the pain of myocardial ischemia.⁷ The cases we present suggest that N_2O may be associated with the development of AVJR in some patients. We know of no data that examines whether AVJR occurs more frequently with N_2O /inhalational or N_2O /narcotics, than with oxygen/inhalational or oxygen/narcotics.

In summary, our ten cases demonstrate that N_2O can cause an AVJR in the presence of a narcotic or volatile baseline anesthetic. This study does not allow calculation of how frequently N_2O causes AVJR. It is hoped that future study will reveal that information. Because the use of N_2O is so common, we believe that further studies of its effect on cardiac electrophysiology and dysrhythmias are warranted.

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Periorbital Edema After Atracurium Administration

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Atracurium produces little or no cardiovascular effects from histamine release.^{1,2} However, anaphylaxis,³ bronchospasm,⁴ and local skin reactions⁵ have been described following its use. We describe a case of periorbital edema following the administration of atracurium.

REPORT OF A CASE

A 10-yr-old female (40 kg) presented for strabismus repair of her right eye on 5/13/86. The patient had undergone general anesthesia on three previous occasions without any complications. Three months prior to the current surgery, she received meperidine (2 mg/kg iv) and diazepam (0.25 mg/kg iv) during a colonoscopy and developed hives around the iv site. There was no associated bronchospasm or hypotension. Although there was a positive family history of atopy, the patient's mother stated that her daughter had no hayfever, asthma, or food or drug allergies.

On the day of surgery, the patient was not premedicated, and anesthesia was induced with thiopental (5 mg/kg iv) and 50% nitrous oxide in oxygen. Atracurium (0.5 mg/kg iv) was then administered over 30 s to facilitate endotracheal intubation. Thirty to 45 s after administration of these drugs, and following intubation, facial flushing was evident. Within 4 min, during the administration of isoflurane (1.5%), flushing progressed to the arms and upper chest with associated periorbital and conjunctival edema. Within 15 min, severe periorbital, conjunctival, and lid edema were present in spite of the administration of 30 mg of iv diphenhydramine. Vital signs were stable throughout this period, and there was no evidence of bronchospasm. Anesthesia was maintained with 50% nitrous oxide in oxygen and 1.5% isoflurane.

The surgeons decided not to proceed with the strabismus repair because the periorbital edema would make it a technically difficult

procedure. Laryngoscopy was performed prior to extubation and revealed mild pharyngeal and vocal cord swelling that was treated with nebulized racemic epinephrine in the recovery room. Although flushing and conjunctival edema persisted for several hours, there was no evidence of respiratory distress or stridor. The patient was observed overnight in the recovery room because of the potential for recurrence of the laryngeal edema. Following an uneventful night, she was discharged. Periorbital edema persisted for 7-8 days.

One month later, the patient returned for further investigation of the cause of the reaction and the drug responsible. Intradermal testing of thiopental and atracurium was performed according to Fisher's protocol.⁶ Histamine (.01%) and 0.9% saline were used as controls. The injection of histamine (0.01 ml) produced a 3-mm wheal and flare, while the injection of saline produced no response.

Immediately prior to testing, thiopental (2.5% solution) and atracurium (10 mg/ml) were diluted by injection into preservative-free normal saline. The dilutions used were atracurium 1:1000, 1:100, and thiopental 1:1000, 1:100. Skin responses were read 30 min after intradermal injection of sufficient solution to raise a 1-2-mm wheal. Injection of thiopental produced no response, while both dilutions of atracurium produced responses greater than that of the histamine control. Atracurium 1:1000 triggered a 7-mm wheal and atracurium 1:100 a 9-mm wheal, both persisting for more than 60 min.

DISCUSSION

This patient's positive intradermal reaction to atracurium 1:1000 suggests a type I hypersensitivity reaction. Although a positive intradermal reaction is usually greater than or equal to 1.0 cm, a wheal of 7 mm can be considered positive if it persists longer than 30 min and is greater than the wheal produced by the control.⁷ However, a type I hypersensitivity reaction requires previous exposure to the drug and classically involves IgE antibodies bound to mast cells.⁸ Thus, the mechanism of sensitization in this patient is unknown, as two of the previous general anesthetics occurred prior to the availability of atracurium and the third involved administration of succinylcholine, pancuronium, isoflurane, and thiopental. Her sensitization may be related to the previously reported phenomenon of crossed anaphylaxis.⁹⁻¹³ Some patients develop antibodies to muscle relaxants to which they have not been

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