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Safety of Inhalation of a 50% Nitrous Oxide/Oxygen Premix

A Prospective Survey of 35 828 Administrations

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Abstract

Background: A 50% nitrous oxide/oxygen (N_2O/O_2) premix is widely used to alleviate pain or anxiety during brief care procedures in various medical domains. In some countries, recent changes in regulation status for medical gases state that they should be considered as drugs. Consequently, more valuable data gained from exhaustive clinical surveys are needed. This prospective study, conducted in the same conditions imposed for testing a drug, aims to analyse the factors that affect tolerance of the 50% N_2O/O_2 premix in a wide range of clinical indications.
Methods: In a 4-year prospective survey, 35 942 data sheets were received from 191 French hospital paediatric (82%) and adult units (18%). Of these, 35 828 sheets were sufficiently complete to be included in the study. The number and the type of adverse events declared to the manufacturer were analysed.
Results: A total of 1581 (4.4%) adverse events were reported on 1384 data sheets, which were mostly gastrointestinal and neuropsychiatric disorders (86%). The main factors associated with adverse events were age, concomitant drug administration and longer duration of inhalation. Among the 27 (0.08%) reported serious adverse events, only 9 (0.03%) were possibly attributed to the N_2O/O_2 premix. Among the serious adverse events that were not attributed to the gas, a concomitant drug association and insufficient patient surveillance occurred in 12 and 2 cases, respectively.
Conclusion: This survey confirms the pharmacological safety of the 50% N_2O/O_2 premix in a wide variety of clinical indications and emphasises the need for rational training of medical personnel in its administration.

Background

A mixture of nitrous oxide (N_2O) and oxygen (O_2) has both sedative and analgesic properties. The 50% N_2O/O_2 premix was proposed for the first time in 1961[1] and its advantages are linked to its simplicity of use and, thus, to a rapid onset of action compared with the two-bottle device. Recovery time was shown to be equally rapid with the one- as with the two-bottle system and safety of administration

was shown not to be affected.[2] The excellent safety record of the one-bottle system led to the introduction of the 50% N_2O/O_2 premix for use by medical personnel other than anaesthesiologists. It has been extensively used in many countries to cover moderate pain and anxiety for out-patient care in paediatrics, bronchoscopy, obstetrics, oncology, dentistry and emergency units.[3-10] However, in many cases the conditions for its use remain insufficiently regulated, particularly in relation to recent changes in nomenclature and regulation status for medical gases.

At their introduction, the medical gases were not assigned to be tested under the same conditions as standard pharmacological drugs, despite the fact that they are also used for therapeutic reasons. The conditions for the use of medical gases vary greatly between countries, clinical indications and practitioners. In many countries, the current trend is to change the status of the medical gases to therapeutic drugs to better regulate use and improve safety.

The pharmaceutical status given to the 50% N_2O/O_2 premix varies between countries. In the US it is considered to be a medical gas, whereas in the UK, Australia, Canada, Benelux and France the mixture has recently been recognised as a drug. Other countries, such as Spain, Switzerland, Greece, Portugal, Scandinavia and Germany, are also likely to change their nomenclature in the near future. This change induces profound modifications in the legislation related to use of the product. First, the manufacturer is obliged to reorganise the conditioning and distribution of the gas to enhance safety. Secondly, the use of a drug implies access to a body of knowledge gained from consecutive surveys and trials conducted in all the different clinical fields of its use.

Within its historical context, most available research into the 50% N_2O/O_2 premix was undertaken without reference to the modern rigorous research conditions imposed for testing a drug. Some previous studies have been conducted using large samples, but these have always been limited to specific domains, such as paediatrics or dentistry.[7,8] Moreover, for medical gases, particular attention should be paid to differences in pharmacological tolerance between methods of administration.

This prospective study aims to describe and analyse the prevalence of adverse effects observed during 35 828 administrations of the 50% N_2O/O_2 premix over a wide range of clinical indications.

Methods

The European Drug Agency decision that medical gases be considered as drugs was adopted by the French Drug Agency – l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFFSAPS) in 1995. A period of consecutive survey for all use of any medical gas followed this decision. This epidemiological survey is based on the data sheets recorded prospectively over the 3½-year period of the temporary license delivered by AFFSAPS (from June 1998 to January 2002) for the 50% N_2O/O_2 premix product Kalinox® [1] (Air Liquide *Santé* International).

Data Collection

The temporary license of use obliged systematic completion of a data sheet after each administration of the product. An example of the data sheet is given in figure 1. The data sheets were supplied with the gas cylinders at each hospital unit. A data sheet had to be completed for each administration regardless of the occurrence or not of an adverse event.

The types of adverse events were described according to the note for guidance on clinical safety data management.[11] Expedited reporting of any serious and/or unexpected adverse event was mandatory, whether considered to be linked to the gas or not. The expedited reporting form included (i) patient details (initials, age, sex, height, weight, medical history); (ii) a description of the premix (brand name, dosage, route of administration, starting date and time, stopping date and time, indications for which the product was prescribed); (iii) a description of any concomitant drugs (as for point ii); and (iv) details of the adverse event (full description of the reaction including body site and severity,

1 The use of trade names is for product identification purposes only and does not imply endorsement.

duration of the event, correlation of disappearance and recurrence of the reaction with stopping and reintroducing the drug, recovery and sequelae conditions). Fatal and life-threatening unexpected events were reported to the regulatory agency.

Patients

Among the 35 942 data sheets collected from 191 hospital units, 82% concerned paediatric interventions and 18% were from adult units. The distribution of patients by age was 3% for 0–1 years, 23%

HOSPITAL AND SERVICE	*to be completed by the pharmacist*
Hospital: *name and address*	Stamp of the pharmacy department:
……..	……..
……..	Number of the prescription form book:……
PRESCRIPTION	*to be completed by the physician*
SERVICE:…….	DATE:……
NAME OF THE CONSULTANT……..	
PATIENT	
NAME: |__|__|__| FIRST NAME: |__|__| DATE OF BIRTH: |__|__| |__|__| |__|__|__|__|	
GENDER: F ☐ M ☐	OR AGE |__|__| years
CLINICAL INDICATION - ADMINISTRATION	
ANALGESIA DURING EMERGENCY: Traumatology ☐ Burns ☐	
ANALGESIA FOR BRIEF PAINFUL PROCEDURES *(adults and children)*	
Lumbar puncture ☐ Bone-marrow aspiration ☐ Minor superficial surgery ☐	Burns dressing ☐ Reduction of uncomplicated fractures ☐ Reduction of peripheral luxations ☐	Venous puncture in children ☐
DURATION OF ADMINISTRATION (min): |__|__|	
ADMINISTRATION REITERATED: YES ☐ NO ☐	
DRUG ASSOCIATION: YES ☐ NO ☐	
IF YES, specify:……..	
OBSERVED ADVERSE EVENTS	
SERIOUS AND/OR UNEXPECTED ADVERSE EVENT(S): YES ☐ NO ☐	
If Yes, complete the form for expedited reporting and address it to the safety department of the manufacturer of the gas.	
NON SEVERE AND/OR EXPECTED EVENT(S): YES ☐ NO ☐	
IF YES, specify:……..…. ……..	
DATA SHEET NUMBER …….	

Fig. 1. Reproduction of an English translation of the data form. For any premix administration, a data sheet was completed in triplicate. One copy was kept inside the medical file of the patient, one was registered at the hospital pharmacy department and the third one was sent to the safety department of the premix manufacturer.

for 1–4 years, 36% for 5–10 years, 22% for 11–18 years, 13% for 19–65 years and 3% for >65 years.

Administration Procedure

The gas cylinders contain an equimolar concentration of N_2O/O_2 and were supplied with a Summary of Product Characteristics document, which specified the indications and contraindications of the gas (contraindications are intracranial pressure, altered consciousness, pneumothorax, emphysema, gas emboli, diving accidents, gaseous abdominal distension and fracture of facial bones).

The N_2O/O_2 mixture was prescribed by physicians and administered either by physicians or nurses through a pressure-reducing valve with a facial mask, chosen in relation to the morphology of the patient. The accompanying instructions stated that the gas should be administered for at least 3 minutes before starting the procedure and should not be inhaled for >30 minutes. Systematic reoxygenation at the end of the administration was not required and thus not checked. However, monitoring of O_2 saturation was recommended. Moreover, recommendations stated that administration should stop if verbal contact with the patient was lost.

Data Management and Statistical Analysis

Data sheets were regularly returned to the premix manufacturer. They were individually checked and registered after double capture. Data management was conducted in accordance with good clinical practice. A chi-squared (χ^2) test was used to test the factors affecting the adverse events.

Results

Among the 35 942 collected data sheets, 114 could not be included in the analysis because of missing information. Thus, a total of 35 828 data sheets are included in the study. On 1384 data sheets, at least one adverse event was reported (3.9% of the total number of data sheets), with a total of 1581 (4.4%) adverse events. Most of the adverse events were classified as gastrointestinal system disorders (45.5% of all adverse events), predominantly vomiting and nausea, and nervous system and psychiatric disorders (40.7%), which were mainly agitation and euphoria. Of all adverse events reported, vomiting was the most frequent (1.4% of all data sheets).

Serious Adverse Events

A total of 27 (0.08%) serious adverse events were reported, relating to 23 patients. A drug had been administered concomitantly for 12 of these 23 patients (52%) and gas inhalation lasted between 1 and 18 minutes. Among the 27 serious adverse events, only 9 (0.03%) were reported as having a reasonable causal relationship with the gas: consciousness disorder (n = 1); vomiting (n = 2); bradycardia (n = 1); vertigo (n = 1); headache (n = 1); nightmares (n = 1); sweating (n = 1) and somnolence (n = 1). Among the 18 serious adverse events that were reported as having no causality with the premix were disorders of consciousness (n = 4); O_2 desaturation (n = 4); apnoea (n = 5); laryngospasm (n = 1); convulsions (n = 2); cardiac arrest (n = 1) and narcolepsia (n = 1). Of these, the two most clinically important (one case of cardiac arrest and one case of O_2 desaturation) were linked to both inappropriate use of the administration device and insufficient surveillance.

Relationship between Clinical Indication and Adverse Events

The most frequent clinical indications for use of the prefixed N_2O/O_2 mixture were minor superficial surgery (45.0%), lumbar puncture (13.5%) and venepuncture (9.7%) for children, and reduction of luxation (19.1%), minor superficial surgery (17.1%), obstetrics (16.9%) and bone-marrow aspiration (9.1%) for adults. For the most frequent indications reported in table I, the rate of adverse events was more homogenous in paediatric (2.4–5.9%) than in adult units (0.2–6.5%). Although the clinical indications of bronchopulmonary endoscopy only concerned 0.9% of paediatric cases and 0.4% of adult cases, the adverse events for this indication were 14.1 and 8.3%, respectively.

Table I. Number of adverse events associated with conscious sedation and analgesia with the prefixed equimolar nitrous oxide/oxygen mixture according to clinical procedure (reported at a frequency of ≥2% of data sheets)

Procedure	Pediatric units		Adult units	
	number of data sheets	number (%) of adverse events	number of data sheets	number (%) of adverse events
Minor superficial surgery	13 252	625 (4.7)	1089	71 (6.5)
Lumbar puncture	3964	173 (4.4)	331	14 (4.2)
Venous puncture	2849	104 (3.7)	61	1 (1.6)
Bone-marrow aspiration	1563	62 (4.0)	579	14 (2.4)
Reduction of luxation	438	23 (5.3)	1217	62 (5.1)
Burn dressings	1415	50 (3.5)	161	5 (3.1)
Reduction of fracture	914	54 (5.9)	423	13 (3.1)
Gastrointestinal endoscopy	784	19 (2.4)	425	1 (0.2)
Dressing changes	781	33 (4.2)	391	7 (1.8)
Obstetrics	NA	NA	1073	12 (1.1)
Miscellaneous[a]	3511	199 (5.7)	607	39 (6.4)
Total[b]	29 471	1342 (4.6)	6357	239 (3.8)

a Procedures reported at a frequency of <2% of all interventions included ear, nose and throat procedures (adverse events: 3.7% and 10.5% for paediatric and adult units, respectively), trauma (4.7% and 3.8%), urological examination (6.2% and 4.0%), biopsy or arterial puncture (6.5% and 12.5%), bronchopulmonary endoscopy (14.1% and 8.3%) and not specified (4.5% and 10.2%).

b 114 data sheets were not considered for this analysis because of missing information.

NA = not applicable.

Incidence of Duration of Inhalation or Concomitant Drug Administration

The distribution of adverse effects according to the duration of inhalation and to concomitant drug administration is shown in table II. Inhalation lasted ≤10 minutes for 62% data sheets. However, among the 34 240 data sheets collected for duration of inhalation, the proportion of adverse events was significantly higher for longer durations (4.9% vs 4.2%, respectively; $p < 0.01$). Also, the concomitant administration of at least one drug was associated with an adverse effect declaration in 26% of all data sheets. Among the 29 971 data sheets collected for drug association, the number of adverse events increased significantly from 3.9% to 4.9% ($p < 0.001$) when at least one drug was associated.

The most common concomitant drugs were local anaesthetics (44.8%), opioid analgesics (19.1%), sedatives (15.6%), non-opioid analgesics (11.9%) and anxiolytics (5.3%) [table III]. The numbers of adverse events differed significantly according to the class of drug given concomitantly with the prefixed N_2O/O_2 mixture ($p < 0.001$). Adverse events occurred most frequently when anxiolytics were used concomitantly (6.2%). In contrast, concomitant sedatives were associated with only 3.1% of adverse events.

Relationship between Age and Incidence of Adverse Events

Age was significantly associated with the incidence of adverse events ($p < 0.001$), with the following distribution according to age: 1.7% for 0–1 years, 2.3% for 1–4 years, 4.2% for 5–10 years, 5.6% for 11–18 years, 3.6% for 19–65 years and 1.4% for >65 years.

Discussion

This study demonstrates the safety of administration of a 50% N_2O/O_2 premix for a wide variety of painful procedures in children and adults, with only 0.03% of all data sheets reporting serious adverse events with a reasonable causality with the use of the premix. It is the largest prospective pharmacological trial yet reported on safety and conditions of use of this premix gas, when considered as a drug, and thus gives valuable data for those countries considering revision of the status of the medical gases.

This study reports an incidence of 4.4% adverse events, with the most frequent adverse events being nausea/vomiting and agitation/euphoria, which accounted for 87% of all such events. This distribution of adverse events is in accordance with other reports on the safety of a 50% N_2O/O_2 premix. A previous study of 7511 premix administrations over 18 months in a paediatric population[7] reported a rate of 6.8% adverse events, whereas a prospective multicentre study of 1205 administrations in dental patients with special needs gave a 5% incidence rate of adverse events.[8] However, other studies have reported higher rates of adverse events for prehospital care of patients of all ages (20.6%)[12] and in paediatric units (37.2%, of which 20.1% experienced euphoria).[13] This discrepancy most probably reflects differences in data collection. In the latter study, adverse events were prelisted and systematically searched for, whereas in the two previously cited surveys, the adverse events were collected in an open field on the data sheets.[7,8] Consequently, some expected adverse events, such as euphoria and somnolence, which are not necessarily unwelcome as long as they remain moderate, were probably not declared as adverse events in this survey. However, this study does not report all the adverse effects of the use of the N_2O/O_2 premix. In particular, it does not include the evaluation of the potential effects of occupational exposure on the personnel who administer the gas.

The incidence of adverse events increased significantly when another drug was administered concomitantly with the N_2O/O_2 premix. In this study, inhalation of the prefixed mixture with anxiolytics was associated with 6.2% adverse events and 3.1% when associated with sedatives. It has been found previously that patients experienced more major adverse events when they received a combination of a benzodiazepine and an opioid analgesic.[7] However, it is not easy to conclude whether the incidence of adverse events was most affected by the concomitant drug itself, by drug interactions, or by patient-related factors, such as their health problems. Other controlled trials are needed to explore the effects of drug associations both on the efficacy and the tolerance of the premix.

The incidence of adverse events increased slightly but significantly (from 4.2% to 4.9%) when inhalation lasted >10 minutes, whereas a previous study did not report any difference according to duration of gas inhalation.[13] It remains to be deter-

Table II. Distribution of adverse events (reported at a frequency ≥0.2% of data sheets) according to system organ class during conscious sedation and analgesia with the prefixed equimolar nitrous oxide/oxygen mixture as a function of the duration of inhalation and concomitant drug administration

Adverse Event	All adverse events [n (%)]	Duration of inhalation [n (%)]		Concomitant drug administration [n (%)]	
		≤10min	>10min	yes	no
Gastrointestinal-system disorders	**720 (45.5)**	**410 (43.6)**	**279 (48.1)**	**140 (43.2)**	**413 (45.3)**
vomiting	529 (33.5)	302 (32.1)	208 (35.9)	101 (31.2)	294 (32.3)
nausea	165 (10.4)	88 (9.4)	66 (11.4)	37 (11.4)	97 (10.6)
others	26 (1.6)	20 (2.1)	5 (0.9)	2 (0.6)	22 (2.4)
Nervous system and psychiatric disorders	**643 (40.7)**	**389 (41.3)**	**232 (40.0)**	**127 (39.2)**	**376 (41.3)**
agitation	121 (7.7)	65 (6.9)	51 (8.8)	28 (8.6)	71 (7.8)
euphoria	96 (6.1)	50 (5.3)	42 (7.2)	16 (4.9)	47 (5.2)
headache	78 (4.9)	45 (4.8)	28 (4.8)	12 (3.7)	51 (5.6)
vertigo	82 (5.2)	62 (6.6)	18 (3.1)	12 (3.7)	53 (5.8)
others[a]	266 (16.8)	167 (17.7)	93 (16.0)	59 (18.2)	154 (16.9)
Other disorders	**218 (13.8)**	**142 (15.1)**	**69 (11.9)**	**57 (17.6)**	**122 (13.4)**
Total	**1581 (100)**	**941 (100)**	**580 (100)**	**324 (100)**	**911 (100)**
No. of collected data sheets	*35 828*	*22 404*	*11 836*	*6612*	*23 359*
Percentage of events	*(4.4)*	*(4.2)*	*(4.9)*	*(4.9)*	*(3.9)*

a Adverse events reported at a frequency <0.2% of data sheets included anguish, mood disorders, paresthesia and somnolence.

Table III. Adverse events according to drug(s) administered concomitantly with the prefixed equimolar nitrous oxide oxygen mixture (reported at a frequency ≥1%)

Concomitant drug	Number of uses of concomitant drugs [n = 14 063][a]	Number (%) of adverse events [n = 647][b]
Anxiolytics[c]	741	46 (6.2)
Local anaesthetics	6301	311 (4.9)
Opioid analgesics	2685	130 (4.8)
Non-opioid analgesics	1678	65 (3.9)
Sedatives[d]	2187	67 (3.1)
Miscellaneous[e]	471	28 (5.9)

a Total number of times use of concomitant drugs was reported.

b Total number of adverse events reported with concomitant drugs.

c Anxiolytics were hydroxyzine, diazepam (as a single agent or associated to a eutectic mixture of local anaesthetics or lidocaine), and dipotassium clorazepate.

d Sedatives were midazolam (as a single agent or in association with either fentanyl, morphine, nalbuphine, lidocaine or paracetamol [acetaminophen]), flunitrazepam and barbiturates.

e Drugs reported at a frequency of <1% included NSAIDs (adverse events: 3.2%), antibacterials (7.0%), antispasmodics (9.4%), chemotherapy (8.8%), oxytocin (2.7%) and miscellaneous (11.3%).

mined whether the increased frequency of adverse events during longer procedures is the consequence of increased exposure to N_2O or to the duration of the procedure itself. Indeed, more adverse events could also result from prolonged procedures causing pain and discomfort. This could be the case during bronchopulmonary endoscopy, which was associated with 14% of adverse events in children in this study. On the other hand, some adverse effects such as nausea and vomiting are directly attributable to N_2O inhalation.[14]

Serious adverse events were rarely reported (0.08%), thereby confirming the previous findings of Gall et al.,[7] who reported a rate of 0.33%. O_2 desaturation occurred in four cases (0.01%). The pertinence of O_2 administration following the use of N_2O/O_2 has been widely debated. In another study, 8 out of 90 (8.9%) children inhaling N_2O at various concentrations (ranging from 50% to 70%, with at least 30% O_2) developed O_2 desaturation (defined as SaO_2 <95%).[15] Other studies have shown no cases of diffusion hypoxia after inhalation of N_2O/O_2 as a single agent either with a single-bottle system[16] or with a two-bottle system at a concentration of <70% N_2O.[17-19] It seems that the hypoxia reported following general anaesthesia with N_2O is most likely to be due to an association with the opioids leading to respiratory depression rather than to the N_2O in itself.

Amongst the life-threatening events, two cases were due to insufficient surveillance. In one case, the patient was restrained under the mask while the bottle remained unopened; in the other case, the patient was left without surveillance whilst he vomited into the mask. The obvious apparent safety of the premix could make the administration of the gas a trivial matter, and hence reduce surveillance. Thus, even though the number of serious events was small, the necessity for appropriately trained teams and protocols should be considered.

Conclusion

This is the largest prospective pharmacological trial yet reported on safety and conditions of use of a N_2O/O_2 premix when considered as a drug and, thus, gives valuable data for those countries considering revision of the status of the medical gases. This survey confirms the pharmacological safety of a 50% N_2O/O_2 premix. However, the study underlines the need for specific, rationalised training in the use of the N_2O/O_2 premix, in particular for non-anaesthesiologists. Medical teams should be trained specifically according to the clinical domain for administration and training should emphasise the need for patient surveillance.

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