Adverse events of premixed nitrous oxide and oxygen for procedural sedation in children

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In France, administration of premixed 50% nitrous oxide and oxygen for procedural sedation is under close supervision by the French Drug Agency before final approval for use. We have examined the frequency of adverse events in children sedated with 50% nitrous oxide and oxygen over a broad range of non-specialised facilities. A mean of 0.33% (SD 0.10) children had major adverse events. Thus, premixed 50% nitrous oxide and oxygen seems to be a safe option for procedural sedation in children.

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The number of paediatric procedures in which sedation or analgesia is used has increased greatly over past years together with reports of mishaps and life-threatening complications. Although several guidelines have been published, there is little agreement on which drugs can be safely given in a non-specialised environment. Sury and colleagues1 have shown that oral sedation with chloral hydrate or benzodiazepine supervised by specialised nurses is effective and safe for diagnostic imaging. Yet the safety of regimens suitable for painful procedures seems less well established.2-4

Nitrous oxide is an anaesthetic gas with analgesic properties. The panel lists contraindications for its use. In France, the government has not yet approved the premixed cylinder of 50% nitrous oxide in oxygen for use as a medical drug. A temporary licence was delivered in March, 1998, by the French Drug Agency (Agence Française de Sécurité Sanitaire des Produits de Santé), with strict guidelines for use of this combination by non-doctors. Administration by non-doctors was restricted to nurses who had attended training sessions. The guidelines also restricted use to children older than 4 years who were not receiving psychotropic drugs. The French Drug Agency further recommends that nitrous oxide be administered for 3 min before the start of the procedure and that total duration does not exceed 30 min. All administrations of premixed 50% nitrous oxide in oxygen have to be declared on a standardised form that records data from the procedure, associated medications, and adverse events. We prospectively collected all such data from patients aged younger than 19 years from 46 institutions to which AGA Medical provided the cylinders, with premixed 50% nitrous oxide in oxygen.

**Absolute contraindications for administration of nitrous oxide**

Patients with:
- Intracranial hypertension
- Unconsciousness
- Pneumothorax
- Other disorders involving accumulation of gas in closed body space (eg, intestinal ileus, sinusitis)

**Contraindications for administration by non-doctors**

- Children younger than 4 years
- Children on psychotropic drugs
- Children with an underlying condition that might impair respiratory or brain function

Declaration sheets were individually checked and registered in hospital pharmacies. Two physicians trained in paediatric anaesthesiology reviewed the data. Premixed 50% nitrous oxide in oxygen was given on 7 511 occasions. The indications were emergency department procedures including laceration repair, fracture reduction, cast remodelling, abscess drainage (n = 2 095); lumbar puncture (1 559); dressing changes (1 315); bone-marrow aspiration
(976) ; flexible bronchoscopy (471) ; gastroscopy (275) ; venous puncture (264) ; and miscellaneous (556) including renal or liver biopsy, bladder catheterisation, and placement of nasogastric tube. Major adverse events were classified as follows: respiratory (eg, oxygen desaturation, airway obstruction, apnoea) and cardiovascular (eg, bradycardia), and oversedation—loss of verbal contact during the procedure or persistence of sedation for longer than 5 min after discontinuation of the anaesthetic. Common side-effects of nitrous oxide, such as euphoria, nausea, vomiting, dizziness, or paraesthesias, were classified as minor adverse events.

7 511 data sheets were collected over 18 months. The total inhalation time ranged from 3 min to 50 min, with a mean of 11 min (SD 6·6). Major adverse events occurred in 25 procedures. All events resolved within minutes after discontinuation of nitrous oxide inhalation. No patient needed intervention to maintain their airway. The table shows frequency of major and minor adverse events. 75 procedures (1·0 %) were cancelled because of inadequate sedation, side-effects, or both.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of cases</th>
<th>Minor adverse events</th>
<th>Major adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency-department procedures*</td>
<td>2 095</td>
<td>136 (65 %)</td>
<td>7 (0,3 %)</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>1 559</td>
<td>76 (49 %)</td>
<td>4 (0,3 %)</td>
</tr>
<tr>
<td>Dressing changes</td>
<td>1 315</td>
<td>67 (51 %)</td>
<td>10 (0,8 %)</td>
</tr>
<tr>
<td>Bone-marrow aspiration</td>
<td>976</td>
<td>30 (31 %)</td>
<td>1 (0,1 %)</td>
</tr>
<tr>
<td>Flexible bronchoscopy</td>
<td>471</td>
<td>24 (51 %)</td>
<td>3 (0,6 %)</td>
</tr>
<tr>
<td>Gastroscopy</td>
<td>275</td>
<td>5 (18 %)</td>
<td>0</td>
</tr>
<tr>
<td>Venous puncture</td>
<td>264</td>
<td>17 (64 %)</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous†</td>
<td>556</td>
<td>20 (36 %)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7 511</td>
<td>375 (50 %)</td>
<td>25 (0,3 %)</td>
</tr>
</tbody>
</table>

*Examples include laceration repair, fracture reduction, cast remodelling, abscess drainage.†Examples include renal or liver biopsy, bladder catheterisation, placement of nasogastric tube.

Adverse events associated with sedation by premixed 50 % nitrous oxide and oxygen

The main factor affecting the rate of major adverse events, as determined by \( \chi^2 \) analysis, was age (\( p = 0,0001 \)). In children younger than 1 year, three of 132 (2,03 %) had major adverse events, compared with 22 of 7 311 (0·3 %) older children (five of 2 294 [0,02 %], seven of 2 573 [0,03 %], and ten of 2 444 [0·4 %], in children aged 1-4, 5-10, and 11-18, respectively; \( p = 0,0001 \)). The rate of major adverse events was also associated with administration of psychotropic drugs in addition to premixed 50 % nitrous oxide in oxygen. Children who were given both a benzodiazepine and an opioid (\( n = 107 \)) had significantly more major adverse events than children receiving no concomitant medication (\( p = 0,004 \)). No significant difference was recorded for children receiving either a benzodiazepine or an opioid alone compared with those who had no concomitant medication (\( p = 0,0053 \)).

Our results suggest that premixed 50 % nitrous oxide in oxygen can be used to sedate children safely during painful procedures, with a 0·33 % rate of potential life-threatening events. This rate is close to that recorded for other classes of sedative agents in children.2 4 Safe administration of premixed 50 % nitrous oxide in oxygen is improved if nurses have appropriate training. The French Drug Agency, in keeping with the American Society of Anesthesiologists' recommendations, has declared that nurses who deliver nitrous oxide should receive appropriate instruction. In our hospital, instruction was provided by the pain unit team and consisted of two sets of training sessions during which basic principles.
practical methods of nitrous oxide administration were taught. In other institutions, training was provided by anaesthetists, by emergency-care physicians, or paediatricians. Because the proposed training might not be sufficient with regard to basic airway management, nurses are instructed to stop delivery of nitrous oxide if verbal contact is lost or if any unexpected event arises.

The eligibility of patients should also be assessed. The French Drug Agency recommends that delivery of nitrous oxide by nurses is only appropriate in children aged 4 years or older, who do not have an underlying disorder that could impair respiratory or brain function, and who are not taking psychotropic drugs. In all other patients, an anaesthetist or experienced physician should be present. The increased rate of adverse events seen in children younger than 1 year supports this recommendation. That children aged 1-4 years have a rate of adverse events close to that of older children suggests that the recommended threshold for specialist assistance could be lowered to 1 year. The belief that nitrous oxide should only be delivered by doctors is widely held. Our results, however, suggest that premixed 50 % nitrous oxide in oxygen reliably induces conscious sedation, and thus could be a first-line option for sedation of children with no other complications in non-specialised facilities.

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