Post-operative Pain Relief: Comparison of Methadone and Morphine when used concurrently with Nitrous-oxide Analgesia

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A previous study (Parbrook et al., 1964) revealed that a 25% nitrous-oxide mixture would provide more potent analgesia than morphine in the post-operative period. A nitrous-oxide and oxygen mixture may be given alone when the use of adequate doses of narcotic are contraindicated, as, for instance, in certain patients after cardiac surgery or in labour when delivery is imminent. Even better analgesia was obtained by concurrent administration of narcotic and nitrous-oxide mixture, and this additive effect may be due to a different mode of action of the two analgesics (Nickerson, 1950; McKenzie and Beechey, 1962).

Because of the evidence that, in equal dosage, methadone (Physeptone) may be a more potent analgesic than morphine (Isbell et al., 1947, 1948; Troxil, 1948; Christensen and Gross, 1948; Masson, 1962), a trial was planned to see if these reports could be confirmed and to ascertain whether the superiority of methadone was still detectable when the narcotic was administered concurrently with nitrous-oxide therapy.

Method

The method used was similar to that described in previous papers (Parbrook et al., 1964; Parbrook and Kennedy, 1964). Patients after upper abdominal operations have a marked impairment of vital capacity due to wound pain. The improvement of vital capacity which follows administration of an analgesic can be used as a measure of its efficacy (Overholt, 1930).

Comparative vital capacity measurements were taken by a Wright respirometer with a rubber mouthpiece attached and using a nose-clip. The mean of three readings was obtained on each occasion. Pre-operative readings were taken the day before operation, and post-operative readings measured before and after each of the following treatments:

1. Morphine 1 mg./stone (0.157 mg./kg.) intramuscularly one hour before testing.
2. Morphine 1 mg./stone intramuscularly (as 1), followed by nitrous oxide 25% breathed for 10 minutes.
3. Methadone 1 mg./stone intramuscularly one hour before testing.
4. Methadone 1 mg./stone intramuscularly (as 3), followed by nitrous oxide 25% breathed for 10 minutes.

The maximum dose of narcotic used was 10 mg.

Twenty patients under 60 years of age participated in the trial, and the two drugs were given in a different order in consecutive patients. Any patient with a productive cough was omitted from this trial.

The technique in each patient was as follows. Pre-operative vital capacity was measured and his cooperation elicited for the trial. Post-operative vital capacity was measured within 48 hours of operation at a time when no analgesic had been given within the previous four hours. The injection of the first narcotic was then made. One hour later the vital capacity was reassessed, and then a 25% premixed nitrous-oxide-in-oxygen mixture was breathed by the patient for 10 minutes from a pilot's mask, described below. Immediately after inhalation of the gas the vital capacity was again measured.

Approximately five hours after the injection the procedure was repeated with the other narcotic.

Special Pilot's Mask

It appeared desirable for the purposes of this trial to use a system of administration of premixed 25% nitrous oxide which would reduce air dilution to a minimum. In this way one should obtain greater consistency of action of the gas. After comparative trials of several techniques the mask shown in Fig. 1 was used.

The mask has some similarities to that described by McDowall et al. (1965) for oxygen therapy. It gives a comfortable but airtight fit and is worn with an elastic head-harness.

![Special Air Force pilot's mask used in this trial (Aimed Ltd.)](http://www.bmj.com)

![Assessment of analgesia. Mean values of the respiratory restoration factor (R.R.F.) for the four treatments.](http://www.bmj.com)
Inspiratory and expiratory valves are incorporated in the mask, and a special spring-loaded inspiratory valve in the microphone position allows the patient to breathe air should there be any failure of gas-supply. After moistening the gas by passage through a humidifier bottle premixed 25% nitrous-oxide and oxygen mixture is led into a 4-litre reservoir bag attached to the mask. The gas-flow is adjusted to prevent any collapse of the reservoir bag on inspiration, and is usually about 8 litres a minute.

Patients were found to accept this mask readily, and several commented on its comfort during the trial.

**Results**

The results are presented in the form of the respiratory restoration factor (R.R.F.) (Fig. 2). This factor (Bromage, 1955) gives the improvement of vital capacity (V.C.) with the analgesic as a percentage of the improvement one would see if the vital capacity were to return to the pre-operative value. The full formula is as follows:

\[ \text{R.R.F.} = \frac{\text{Analgic V.C.} - \text{Pain V.C.}}{\text{Pre-operative V.C.} - \text{Pain V.C.}} \times 100\% \]

With the use of this formula an R.R.F. of 100% would, ideally, represent total analgesia, whereas an R.R.F. of 0% represents no analgesia. The use of the R.R.F. has a further advantage in that it permits better comparison of results taken at different stages of the post-operative period. The steady improvement of vital capacity during this time produces an extra variable if one uses, as an index of analgesia, a simple percentage improvement or absolute values of vital-capacity improvement.

**Statistical Assessment.** The Results are Expressed in the Form of the Respiratory Restoration Factor

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean Diff.</th>
<th>S.E. of Mean Diff.</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>7.9</td>
<td>3.2</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Morphine</td>
<td>9.9</td>
<td>1.9</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Methadone and nitrous oxide</td>
<td>11.4</td>
<td>1.7</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Morphine and nitrous oxide</td>
<td>13.4</td>
<td>2.5</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

The improvement of vital capacity with methadone was significantly better than that with morphine, both when treatment was with narcotic alone (P < 0.05) and when treatment was associated with nitrous-oxide therapy (P < 0.01) (see Table). As shown in the previous trial (Parbrook et al., 1964), the treatment with nitrous oxide and narcotic was in both instances significantly superior to treatment with narcotic alone (P < 0.001 in each case).

Of particular interest is the greatly superior effect of nitrous oxide and methadone (mean R.R.F. 27.5%) compared with that of morphine alone (mean R.R.F. 8.3%), and from the clinical point of view this was noticed by the majority of patients, who were grateful for this marked relief of pain.

The results were similarly significant when assessed in the form of simple percentage vital-capacity improvement. This varied from 13.1% with morphine alone to 47.7% with methadone-and-nitrous-oxide therapy.

**Discussion**

The results confirm those of previous workers in demonstrating the superiority of methadone over morphine as an analgesic when the drugs are given in the same dosage (1 mg./stone (0.157 mg/kg.) body-weight). An assessment of the comparative value of methadone and morphine is incomplete without consideration of the relative degree of respiratory depression. Scott et al. (1947) reported that methadone appeared to produce less respiratory depression than morphine. A more detailed trial of this aspect by Prescott et al. (1949) indicated that respiratory depression from methadone, 10 mg. intramuscularly, was similar to or possibly less than that from morphine, 10 mg. intravenously when assessed by the ventilatory response to 3% and 5% carbon dioxide.

Methadone has a further advantage in giving less sedation than morphine (Christensen and Gross, 1948; Troyil, 1948), and this can be of value in the post-operative period, when the patient's cooperation is required for physiotherapy. It has also been suggested that there is a lower incidence of nausea and vomiting with methadone than with morphine (Scott et al., 1947; Christensen and Gross, 1948).

The combined use of nitrous oxide and methadone gives a considerable increase of analgesia, the increase of R.R.F. in this trial being at least double that of morphine alone. It might be thought that a similar degree of analgesia could be obtained by raising the dose of methadone or increasing the concentration of nitrous oxide, but there is a risk of respiratory depression if the dose of narcotic is excessive, and, as pointed out in a previous paper (Parbrook and Kennedy, 1964), there is an increased risk of side-effects when nitrous oxide is given continuously and efficiently in concentrations of over 25%. No undesirable side-effects were seen in this trial except in one patient who was feeling slight nausea after operation and in whom administration of 25% nitrous oxide had to be stopped, as he experienced paraesthesia and increase in his nausea. The nausea improved and paraesthesia disappeared after he had ceased to breathe the gas. The only other side-effect noted was that the patients often commented on feeling pleasantly sleepy during inhalation of the nitrous oxide.

Higher concentrations of nitrous oxide such as the standard 50% premixed gas can be administered, of course, provided that the number of breaths taken is limited, the system permits considerable air-dilution, or the patient is exceptionally tolerant of the gas.

**Application of the Technique in Post-operative Physiotherapy**

The use of nitrous-oxide analgesia in the treatment and prevention of "post-operative chest" has been described briefly in a previous paper (Parbrook, 1965a). Post-operative atelectasis, hypoxia, or cough after upper abdominal operations are in part due to abdominal pain, which causes shallow respiration and a reluctance to take deep breaths. Routine therapy by intermittent short-term 25% nitrous-oxide inhalation can be combined usefully, with conventional relief of pain, with methadone as a preparation for physiotherapy. It helps to prevent atelectasis by allowing the patient to take deeper breaths and, alternatively, can be used to permit patients who have developed a cough to clear their secretions. In the latter case the nitrous-oxide analgesia is found to persist for several minutes after each administration of the gas, and this allows time for coughing. During coughing, of course, the abdomen should be supported. Between its use in these patients the mask must be sterilized. The Air Force mask described in this trial can be sterilized by chemical methods, and studies are in progress to produce one which may be autoclaved or boiled.

A similar system of post-operative pain relief for use with physiotherapy has been described by Ellis and Bryce-Smith (1965), who used the inhalation of trichlorethylene. Studies by Dundee and Moore (1960a) and Dundee et al. (1962), however, suggested that nitrous oxide may be preferable, as Trilene may produce an initial antitussive effect or cause after-effects of hangover and lassitude.

Apart from its use in the treatment and prevention of post-operative chest complications it seems likely that the excellent analgesia obtainable from nitrous oxide and methadone will
lead to a much wider use of these combined agents for relief of severe short-term pain from all causes.

Contraindications

The dangers and contraindications of narcotics are too well known to require comment in this paper, but there are three possible special contraindications to the use of nitrous-oxide mixtures.

Klikovich (1881) advocated the use of nitrous-oxide inhalations in the treatment of certain types of nausea and vomiting, but it has been noted on three occasions in the present and previous trials that pre-existing nausea was exacerbated by nitrous-oxide therapy. It would therefore appear wiser to avoid the use of gas in such patients.

Gaseous abdominal distension (Hunter, 1955 ; Eger and Saidman, 1965) provides a relative contraindication to continuous pain relief by nitrous oxide, as even 25% nitrous oxide may cause slight increase of the distension. Because of the relatively small blood-flow to the bowel, changes in volume occur slowly, and consequently short-term administration of 25% nitrous oxide is not necessarily contraindicated.

Finally, continuous treatment with nitrous oxide for more than 24 hours carries special dangers of depression of the bone-marrow and agranulocytosis (Lassen et al., 1956 ; Green and Eastwood, 1963 ; Green, 1964 ; Parbrook, 1965b).

Conclusions

A technique of pain relief utilizing concurrent administration of nitrous oxide and methadone offers a degree of analgesia more than twice as potent as that from conventional morphine therapy with no increase in the incidence of undesirable side-effects. Such therapy should prove valuable in all forms of severe pain and can also be utilized as an aid during routine physiotherapy in patients after upper abdominal operations.

Summary

A trial was conducted to assess the relative analgesic potency of methadone and morphine when administered concurrently with 25% nitrous oxide for post-operative pain relief.

Pain relief was assessed by the improvement of vital capacity in patients after upper abdominal operations, and the four treatments assessed were: (1) morphine 1 mg./stone (0.157 mg./kg.) body-weight one hour before testing; (2) morphine (as 1) followed by 25% nitrous oxide breathed for 10 minutes; (3) methadone 1 mg./stone body-weight one hour before testing; and (4) methadone (as 3) followed by 25% nitrous oxide breathed for 10 minutes. The 25% nitrous oxide was administered from a special premixed cylinder by means of a modified Air Force pilot's mask.

Treatment with methadone was found significantly better than with morphine, both when administered alone or when assessed in conjunction with nitrous-oxide analgesia. In both cases nitrous oxide and narcotic gave significantly better analgesia than narcotic alone. Assessed in terms of vital-capacity improvement, the analgesia from methadone and nitrous-oxide therapy was more than twice as potent as that from morphine alone.

This potent analgesia can be utilized in the post-operative physiotherapy of patients to prevent and treat post-operative chest. By permitting deeper breaths it helps to prevent atelectasis, and, by pain relief, enables patients to cough up retained secretions.

Nitrous oxide is contraindicated in patients with pre-existing nausea. Nitrous-oxide mixtures should also not be given for long periods to patients with severe gaseous abdominal distension, and continuous nitrous-oxide therapy for periods of over 24 hours may carry a risk of bone-marrow depression. Apart from these limitations nitrous-oxide-and-methadone therapy should prove a valuable system of severe pain relief in both post-operative and other patients.

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References


