Papers and Originals

Methoxyflurane and Nitrous Oxide as Obstetric Analgesics. I.—A Comparison by Continuous Administration

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British Medical Journal, 1969, 3, 255–259

Summary: Methoxyflurane and nitrous oxide have been compared as obstetric analgesics. The inhaled concentrations of these agents, given continuously, were adjusted by an anaesthetist to maintain each patient at the optimum state between reaction to pain and consciousness. Assessments were made continuously.

Though the anaesthetist's assessment showed no difference between the mean results, a greater proportion of the methoxyflurane patients were "satisfactory" for 90–100% of the time than of the nitrous oxide patients, particularly in regard to objective pain relief. The midwives' opinion of those who had "complete" pain relief supported this. Nausea was significantly less among methoxyflurane patients, and vomiting during labour occurred only in patients who had nitrous oxide. It is concluded that nitrous oxide and methoxyflurane given in a continuously adjusted concentration are almost equally effective as obstetric analgesics, though there are certain features which favour methoxyflurane.

Introduction

An objective method of assessment showed methoxyflurane to have some advantages over trichloroethylene as an obstetric analgesic (Major *et al.*, 1966). Since nitrous oxide is also widely used, any new inhalational analgesic must also be compared with it. The present investigation involving equally few patients compares the effects of methoxyflurane with those of nitrous oxide for the relief of pain in labour in the same manner as in our earlier trial.

The effectiveness of two drugs can be properly compared only when the "optimum" dose of each is used. The optimum dose is that which provides the maximum therapeutic effect with an incidence of side-effects acceptable in the clinical circumstances. The administration of an inhaled drug for the relief of pain in labour should provide as great a degree of alertness, and of tranquillity, compatible with an acceptable level of pain relief. Side-effects like nausea and vomiting should be minimal.

Nitrous oxide and trichloroethylene are usually administered intermittently for labour, the mother inhaling for the period immediately preceding and during a contraction, then breathing air in the intervening periods. Because of its low blood solubility the arterial tension of nitrous oxide rises rapidly, and, conversely, when inhalation is discontinued the blood level falls equally rapidly, resulting in an evanescent clinical effect. Methoxyflurane, on the other hand, is much more soluble in blood and tissues. Consequently, when the vapour is inhaled the blood tension rises more slowly, and when the patient

breathes air the fall in blood tension is less rapid than with nitrous oxide. Besides these solubility differences, the clinical effects also depend on the patient's ventilation. The effects of these factors must introduce a considerable variation in the results. The continuous inhalation of the agents in this trial permitted the concentrations to be varied at frequent intervals, so as to maintain as high a level of pain relief as possible, consistent with alertness and co-operation. Valid comparisons can then be made of each agent administered at its optimum concentrations.

Method

Only normal deliveries were included in the trial. Those who had received instruction in psychoprophylaxis or hypnosis were excluded. The choice between nitrous oxide and methoxyflurane was made on a random basis. No restriction was placed on other analgesic or sedative drugs.

Apparatus

The trial was intended to be blind for both the midwife and the patient, and therefore both mixtures were delivered from a single suitably shrouded apparatus. Since the characteristic smell of methoxyflurane rendered it readily recognizable to the midwife, in some random cases when nitrous oxide was being used methoxyflurane was vaporized into the room. It was not possible to make the trial blind for the observer, since he also administered the drugs.

The patient inhaled a known concentration of either nitrous oxide in oxygen or methoxyflurane in oxygen-enriched air from a bag into which there was a continuous flow of the vapour or gas mixture. The concentration could be varied within wide limits by the observer.

Nitrous oxide in oxygen was given from a Walton V anaesthetic apparatus (B.O.C. Ltd.) fitted by us with an enlarged dial. It was calibrated in 5% steps from 20 to 100% oxygen and checked at continuous flows up to 40 l./min. with a paramagnetic oxygen analyser. Leaks in the system, which might have allowed entrainment of air, were sought by analysis for nitrogen by means of a gas chromatograph.

Methoxyflurane was given from a Pentec mark II vaporizer (Cyprane Ltd.) fitted with an oxygen-driven Venturi tube which entrained air. The resulting mixture contained about 40% oxygen.

The vaporizer output was analysed by means of a Pye series 104, model 4, gas chromatograph, which had been calibrated with gravimetric standards. The dial of the vaporizer was marked by us in 0.05% steps.

The patient breathed through a wide-bore tube of a Magill circuit to which either the nitrous oxide or methoxyflurane outflow was connected. The patients were instructed that there

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was no need to hyperventilate. The flows into the bag were about 30 l./min. for methoxyflurane and 40 l./min. for nitrous oxide.

Before inhalation was begun the mother was observed during a contraction, and the response to the contraction and the degree of drowsiness were graded. The inhalation was not started unless the patient responded to each contraction and was not too drowsy from previously administered drugs. Two patients were excluded from the trial on these grounds.

Anaesthetist's Assessment

Observations were made by the anaesthetist throughout the inhalation period. The method of assessment has been described in detail elsewhere (Major *et al.*, 1966). They included the recording, on a carefully defined basis, of the response to each contraction, of the level of consciousness, and of the degree of restlessness occurring between contractions. The proportion of the total time of inhalation for which all these factors were considered to be simultaneously "satisfactory" is then expressed as a percentage of the total period of inhalation (Major *et al.*, 1966). In addition, together with other relevant observations, a continuous record is made of the inhaled concentration of the drug. The concentration is altered only when indicated by the patient's reactions. In particular, excessive drowsiness is an indication for lowering the concentration. In the trial each change was made one step at a time—that is, a 5% change for nitrous oxide and a 0.05% change for methoxyflurane. Steps of these magnitudes were chosen because they lie halfway between concentration differences which have already been shown to produce variations in effects (McAneny and Doughty, 1963; Major *et al.*, 1966, 1967).

Opinions of Midwife and Mother

At the end of labour the opinions of the mother and the midwife were also sought. The mothers were questioned again at 36 to 48 hours.

Results

Randomization

Forty-eight patients received continuous inhalational analgesia in this trial; 24 mothers had methoxyflurane and 24 had nitrous oxide. Each group included 13 multiparous women and 11 mothers having their first labour.

The progress of labour in the two groups was similar, the mean duration of the second stage being 32.0 minutes (S.D. ± 23.4) for nitrous oxide and 36.7 minutes (S.D. ± 25.3) for methoxyflurane. The mean duration of inhalation for the methoxyflurane group was 82.5 minutes (S.D. ± 72.8) and for the nitrous oxide group 83 minutes (S.D. ± 66.3).

The mean age of the nitrous oxide group was 25 years (S.D. ± 5.0) and of the methoxyflurane group 24.4 years (S.D. ± 5.9).

Pethidine was the only other analgesic used. Of the mothers who received pethidine in the four hours preceding the beginning of inhalation 11 were given nitrous oxide and 14 methoxyflurane.

The groups were therefore considered to be comparable in all these respects.

Anaesthetist's Assessment

Reactions to Contractions.—There was no significant difference between the mean values for the two drugs (Table I).

The distribution of the individual cases for "percentage reaction to contractions satisfactory" is shown in Table II. Twelve (50%) of the methoxyflurane group were satisfactory for 90–100% of the time, compared with 5 (21%) of the nitrous oxide group. This difference is statistically significant. Of all the mothers only six were considered "satisfactory" throughout the period of inhalation (100% of the time); five of these had received methoxyflurane.

TABLE I.—Anaesthetist's Assessment of "Analgesia"

Factors Studied	Mean percentage of time satisfactory ± 1 Standard Deviation	
	Nitrous Oxide (24 patients)	Methoxyflurane (24 patients)
All factors satisfactory	70.9% $\pm 17.6\%$	73.8% $\pm 26.3\%$
Reactions to contractions satisfactory	77.2% $\pm 14.7\%$	81.4% $\pm 22.3\%$
Level of consciousness satisfactory	94.5% $\pm 7.2\%$	94.0% $\pm 8.7\%$
Restlessness satisfactory	97.2% $\pm 6.4\%$	92.1% $\pm 14.7\%$

TABLE II.—Distribution of Cases According to Percentage Reaction to Contractions Satisfactory

Drug	Percentage Time Reaction to Contractions Satisfactory				
	0–	60–	70–	80–	90–100
Nitrous Oxide (24 patients) ..	2 (8%)	4 (17%)	8 (33%)	5 (21%)	5 (21%)
Methoxyflurane (24 patients) ..	3 (13%)	3 (13%)	2 (8%)	4 (16%)	12 (50%)

Significance: 90–100%, $P < 0.05$ (Yates's correction).

Consciousness and Restlessness.—The mean percentage of the duration of inhalation for which consciousness and restlessness were considered satisfactory for each group shows no significant difference between the two agents (Table I).

All Factors "Satisfactory."—The percentage of the duration of inhalation for which all factors were simultaneously satisfactory shows no significant difference between the drugs (Table I). The effect of the duration of inhalation and the progress of labour on the analysis of "all factors satisfactory" is shown in Table III. The half-hour period immediately

TABLE III.—Effects of Duration of Inhalation and Progress of Labour on All Factors Satisfactory

Drug	Mean percentage of Time All Factors Satisfactory			Half-hour Period Immediately Before Delivery
	Half-hour periods after beginning of inhalation			
	1st	2nd	3rd	
Nitrous Oxide	71.2% (24)	73.8% (19)	67.5% (11)	66.7% (24)
Methoxyflurane	73.8% (24)	71.2% (17)	62.0% (12)	72.1% (24)
Significance				P > 0.5

Numbers of patients are given in parenthesis.

before delivery may be regarded as coincidental with the second stage of labour, since the mean duration of the second stage was about 34 minutes. It is most important during this period that the mother co-operates fully with her attendants. There is no significant difference between the two agents for any period of this analysis. For the half-hour immediately preceding delivery, however, only 14 cases were satisfactory for all factors for 90–100% of the time. Eleven of these had received methoxyflurane and three nitrous oxide. The difference is statistically significant ($P < 0.05$).

TABLE IV.—All Factors Satisfactory. Effect of Pethidine

Other analgesic	Nitrous Oxide	Methoxyflurane	Significance
Pethidine given within 4 hr. of inhalation	72.9 $\pm 19.0\%$ (11 cases)	67.5 $\pm 29.6\%$ (14 cases)	$P > 0.6$
No pethidine	69.3 $\pm 16.0\%$ (13 cases)	82.6 $\pm 18.8\%$ (10 cases)	$P < 0.1$
Significance	$P > 0.6$	$P > 0.1$	

Effect of Pethidine.—There was little difference between the agents if pethidine had been given in the four hours preceding the onset of inhalation (Table IV). On the other hand, when pethidine had not been used methoxyflurane was satisfactory for 82.6% of the duration of inhalation compared with 69.3% for nitrous oxide.

Opinion of the Midwife

Pain Relief.—The pain relief was considered by the midwife to be "complete" in 9 (38%) of the methoxyflurane group and in 2 (9%) of the nitrous oxide group. This difference is significant ($P < 0.05$). Twenty (83%) of the methoxyflurane group and 15 (65%) of the nitrous oxide group were considered to have had complete or considerable pain relief ($P > 0.2$).

Drowsiness and Restlessness.—In each series three patients were thought to be "too drowsy." Three patients in each group were considered to be restless. A total of five patients were regarded as either too drowsy or restless. Restlessness, in this instance, applies to the midwife's general impression and not to the defined "restlessness between contractions" used by the anaesthetist.

Blood Loss.—The blood loss was estimated by the midwives. The mean loss in the methoxyflurane group was 176 ml. (range 30–500 ml.) and in the nitrous oxide group 160 ml. (range 25–500 ml.).

Opinion of Mother

Assessment of Pain Relief Immediately after Delivery.—All but two mothers were questioned immediately after delivery (Table V). Nineteen in each group thought that the pain relief was complete or considerable. Seven (29%) in the methoxyflurane group thought that the pain relief was complete, compared with 4 (18%) in the nitrous oxide group. Both the patients who were not questioned had received nitrous oxide; one was distressed after delivering a grossly abnormal infant and the other had had the inhalation discontinued early because of severe nausea and repeated vomiting.

TABLE V.—Pain Relief. Mother's Immediate Opinion

Relief from Pain	Nitrous Oxide (22 patients)	Methoxyflurane (24 patients)
Complete	4 (18%)	7 (29%)
Considerable	15 (68%)	12 (50%)
Slight	3 (14%)	4 (17%)
None	0 (0%)	1 (4%)
Total	22 (100%)	24 (100%)

Assessment of Pain Relief at 48 Hours after Delivery.—Of the 16 mothers (33%) who changed their opinion at the second questioning 11 had received nitrous oxide and 5 methoxyflurane. Four of the five methoxyflurane patients thought that the pain relief had been better than they stated earlier compared with 6 of the 11 nitrous oxide patients. At this assessment 19 (83%) of the nitrous oxide patients considered the pain relief to be complete or considerable, compared with 22 (92%) of the methoxyflurane cases.

Opinion of Multiparae.—Eight (62%) of the methoxyflurane patients and 6 (46%) of the nitrous oxide group stated that the labour was better than their previous labours.

Nausea and Vomiting.—Mothers were questioned immediately and at 36 to 48 hours concerning episodes of nausea and vomiting during the labour and in the subsequent 24 hours. Four patients, all of whom had received nitrous oxide, vomited during the labour. Immediately after the delivery 8 (35%) of the nitrous oxide group and 2 (8%) of the methoxyflurane group replied that they had experienced nausea during labour. The difference is almost significant ($P < 0.1$). At 36 to 48 hours after delivery 13 (54%) of the nitrous oxide group and 5 (21%) of the methoxyflurane group had experienced nausea at some

time during labour or in the succeeding 24 hours. This difference is significant ($P < 0.05$). Six (25%) of the nitrous oxide series and 4 (17%) of the methoxyflurane series had vomited. All the patient who vomited also complained of nausea.

Memory of Labour and Delivery.—Mothers were asked 36 to 48 hours after delivery whether they remembered their labour and delivery clearly, hazily, or not at all. There was no important difference between the two groups in this respect.

Smell (36 to 48 Hours after Delivery).—Mothers were questioned concerning smell. Twenty-three (96%) of the methoxyflurane group and 7 (29%) of the nitrous oxide group noted a smell. None found it unpleasant. Several of the nitrous oxide group commented that the smell was either "like being in the dentist's chair" or "like rubber."

Sleep and Dreams.—Mothers were asked whether they had fallen asleep during the labour. Eighteen cases in all (8 nitrous oxide and 10 methoxyflurane) did so. Five (22%) of the nitrous oxide group and 4 (17%) of the methoxyflurane group dreamed while asleep. Two of the nitrous oxide group complained of vivid frightening dreams during labour, though they did not remember this when questioned afterwards.

Other Criteria

Mode of Delivery.—Nineteen (79%) in each group had a spontaneous vertex delivery. Five (21%) in each group required forceps delivery.

Blood Pressure and Pulse.—No untoward effects on either the pulse rate or blood pressure were noted.

Respiration.—There was a tendency for most mothers to hyperventilate during contractions. This tendency was accentuated by the midwife's advice that they should concentrate on their breathing in order to control any premature desire to push during late first stage.

The Baby

There was one case of foetal distress; the mother had received nitrous oxide and was delivered by forceps.

The distribution of the Apgar scores at one minute after delivery shows no significant difference between the two groups. Only one baby was scored Apgar 10, partly because a strict interpretation of the score was made, any slight cyanosis of the extremities being scored as a maximum of 9.

Two neonatal deaths occurred. One had severe osteogenesis imperfecta with multiple rib fractures; the other was a second twin of low birth weight (1.9 kg.) that died of the respiratory distress syndrome.

Concentrations of Analgesics

From the continuous recordings of the inhaled concentration of the drugs the mean concentration for each consecutive 15-minute period was calculated (see Chart).

The number of changes of concentration made by the anaesthetist during each consecutive 15-minute period was also counted and the mean number in each group was calculated (Table VI). For the nitrous oxide group the number of changes

TABLE VI.—Mean Number of Changes in Concentration for Consecutive 15-minute Periods

Drug	Mean No. of Changes of Concentration for Consecutive 15-minute Periods from Start of Inhalation							
	1st	2nd	3rd	4th	5th	6th	7th	8th
Nitrous Oxide ..	2.25	1.91	1.60	1.44	2.73	2.75	1.25	2.00
No. of cases ..	(24)	(23)	(20)	(16)	(11)	(8)	(8)	(7)
Methoxyflurane ..	2.16	1.50	1.71	1.50	1.00	0.75	1.14	0.29
No. of cases ..	(24)	(22)	(17)	(14)	(12)	(8)	(7)	(7)
Significance ..	> 0.5	> 0.1	> 0.8	> 0.9	< 0.05	< 0.1	> 0.1	> 0.5

Mean No. of changes for nitrous oxide for each 15-minute period = 1.96.
Mean No. of changes for methoxyflurane for each 15-minute period = 1.47.

of concentration in each period showed no definite trend, neither increasing nor decreasing during labour, whereas there was a progressive decrease in the number of changes with methoxyflurane.

Mean concentration of inhalational agents for 15-minute periods from onset of inhalation.

Clinical Observations

The patients did not object to having the mask applied continuously. Nitrous oxide provided analgesia but it easily impaired consciousness. It was difficult to produce a state of sedation by increasing the concentration without producing short episodes of semiconsciousness. The patient would then awake in confusion and distress, complaining of unpleasant dreams. Methoxyflurane, on the other hand, induced a somewhat placid state in most mothers, who, while retaining the ability to co-operate, appeared to be detached emotionally from the pain. Several mothers spontaneously compared this to the effects of alcohol. Overdosage produced a progressively more drowsy patient, who sometimes fell asleep between contractions. In contrast to nitrous oxide, this was never associated with distressing dreams, but appeared more like the action of pethidine.

Discussion

This method of comparing these two agents by continuous inhalation of a variable concentration of each (Major *et al.*, 1966) has a particular value because of the different physical characteristics of nitrous oxide and methoxyflurane.

Furthermore, if fixed inhaled concentrations of each agent had been compared, then it could have been argued that any conclusions reached were the result of choosing an incorrect inspired concentration of one or other of the drugs. By continuously adjusting the inhaled concentration in order to maintain the best possible conditions for the patient and the midwife, the effects of changes in ventilation and of periods of inhalation have been largely eliminated, and the potential value of each agent under ideal circumstances are compared.

The results from the anaesthetist's observations show that there is little difference between the average analgesia achieved by either drug (Table I). In respect of objective pain relief,

however, the distribution of the patients with regard to the "reaction to contractions satisfactory" is quite different (Table II). In contrast to the nitrous oxide group, half of the methoxyflurane cases were considered to be satisfactory for 90–100% of the time. The remainder are evenly distributed between 10 and 90% satisfactory. This distribution is to some extent reflected by the midwife's assessment, in which there were significantly more methoxyflurane than nitrous oxide patients who were completely relieved of pain. A study of such factors as parity, use of pethidine, and complications of labour did not show a preponderance in one or other group to account for this distribution pattern.

The effect of pethidine on the observations is somewhat surprising, since this was not apparent in our earlier trials. There seems little doubt in this trial that those patients who had received methoxyflurane alone and who did not have pethidine have a better score of "all factors satisfactory" than those who had been given nitrous oxide alone or either agent and pethidine. Selection of patients could be responsible for the results. Patients who were not given pethidine during the four hours preceding inhalation were clearly those who, in the midwives' opinion, did not require it. It would appear that in these patients methoxyflurane was especially effective. For the patients who did have pethidine methoxyflurane was no different from nitrous oxide.

Nitrous oxide was associated with a higher incidence of nausea and vomiting than methoxyflurane. During labour and the immediate postnatal period there is normally an incidence of nausea and vomiting even in the absence of any drug therapy, and it is well known that pethidine and other analgesics cause an increased incidence of these complications. The use of pethidine, however, was equally distributed between the agents. Our previous two trials (Major *et al.*, 1966, 1967) and the present one show a reasonably consistent incidence of nausea and vomiting for methoxyflurane. During labour, however, the incidence of nausea with methoxyflurane appears acceptably low, ranging from 5 to 13%, and, unlike nitrous oxide or trichloroethylene, vomiting has never occurred.

During both our trials in which methoxyflurane was administered continuously the incidence of nausea throughout both labour and the following 48-hour period was 21% and 32% respectively. In the trial (Major *et al.*, 1967) in which methoxyflurane was administered intermittently and when concentrations of 0.25% and 0.35% were compared, the incidence of nausea was 5% and 26% respectively. Though the total incidence is relatively low there appears to be some dose-effect relationship. On the other hand, with nitrous oxide, 54% of the patients were nauseated at some time during or just after labour and half of these vomited (25%). Parkhouse *et al.* (1960), administering 40% nitrous oxide continuously to unpremedicated volunteers, noted a similar incidence of nausea (59%). These investigators observed that nausea persisted, occasionally for several hours after inhalation had ceased. McAneny and Doughty (1963) found during the period of labour alone an incidence of nausea and vomiting of 16 to 18% with 50% nitrous oxide in oxygen administered intermittently. For 75% nitrous oxide the incidence rose to 22%. Again a dose-effect relationship may be present.

The mean concentration of methoxyflurane administered in this trial was 0.22%, which is the same as that found in our previous trial in which the concentration was controlled by a different observer (Major *et al.*, 1966). This confirms the comparability of the present trial with our previous one and, again, the validity of the concentration of methoxyflurane chosen for intermittent use. The mean concentration of nitrous oxide was 41.2%, given continuously. For intermittent use clearly a higher concentration would be necessary.

In this trial great stress was laid on the prevention of unconsciousness. Nevertheless, with nitrous oxide this was difficult, since when higher concentrations were being given a patient who was alert and co-operative might suddenly

become semiconscious during a period of hyperventilation, returning to her original state when her breathing had reverted to normal.

As labour progressed, the concentration of nitrous oxide used showed little progressive change, whereas that for methoxyflurane fell (see Chart). The number of changes of concentration in each 15-minute period fell with methoxyflurane, whereas there was no consistent change with nitrous oxide. With methoxyflurane the fall in concentration and the number of changes of concentration correspond with what we would expect from the relationship between the inhaled and blood concentrations.

The effects of 0.35% methoxyflurane given intermittently have already been investigated (Major *et al.*, 1967) and were similar to those demonstrated in the present trial. It was, however, more difficult to maintain the "analgesic" state with continuous nitrous oxide, and, since there is some doubt in our minds whether the best concentration of nitrous oxide is

in fact 50%, we propose to investigate whether intermittently administered nitrous oxide is as effective as when it is administered continuously.

We would like to thank the obstetricians and midwives of the Cardiff Maternity Hospital for their help and co-operation. Two of us (P. L. J. and E. V. J.) were the grateful recipients of financial support as Research Fellows from the Board of Governors of the United Cardiff Hospitals. We are also grateful to Abbott Laboratories Ltd. for supplies of methoxyflurane.

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Methoxyflurane and Nitrous Oxide as Obstetric Analgesics. II.—A Comparison by Self-administered Intermittent Inhalation

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British Medical Journal, 1969, 3, 259–262

Summary: Methoxyflurane (0.35%) in air and nitrous oxide/oxygen (50%/50%) self-administered intermittently in the usual way have been compared as analgesics for labour. There were 25 patients in each group. Objective assessment by an anaesthetist showed that methoxyflurane is the more effective analgesic, and this was supported by the opinion of the multiparae. Nausea and vomiting were significantly less with methoxyflurane. Fifty per cent. nitrous oxide in oxygen given intermittently does not appear to be the best analgesic concentration. Nevertheless, since a considerable variation in sensitivity exists, it would probably be unwise to consider the introduction of higher concentrations for use by unsupervised midwives.

This trial confirms the predictions made by us using a method for screening inhalational analgesics, in which methoxyflurane and nitrous oxide were given continuously.

Introduction

A method of assessing obstetric analgesics which requires few patients showed that methoxyflurane had several advantages over trichloroethylene (Major *et al.*, 1966). The agents are administered continuously and the inhaled concentrations adjusted in order to maintain a balance between pain relief and excessive sedation. Because methoxyflurane and trichloroethylene have similar solubilities it can be assumed that these clinical differences will be present when the agents are given intermittently in the usual manner. Jones *et al.* (1969), using this method, have demonstrated moderate differences between methoxyflurane and nitrous oxide, generally in favour of

methoxyflurane. It would seem that intermittent inhalation should favour methoxyflurane, since nitrous oxide is comparatively insoluble, and the timing of intermittent inhalations is important. Furthermore, methoxyflurane has already been shown to give similar results when used either intermittently (Major *et al.*, 1967) or continuously. We cannot be sure that a prediction of drugs with such different solubilities in blood and tissue would be confirmed in practice. This trial therefore studies the agents administered intermittently.

The concentration of nitrous oxide in oxygen used was 50%, since this is the one recognized for use by unsupervised midwives. The optimum concentration of methoxyflurane for intermittent inhalation has been found to be 0.35% (Major *et al.*, 1967). These concentrations were therefore compared.

Method

Only normal deliveries were included in the trial. Those subjects who had received instruction in psychoprophylaxis or hypnosis were excluded. Other analgesic or sedative drugs were given by the midwife on her usual indications. The choice between nitrous oxide and methoxyflurane was made on a previously randomized basis. During the first stage of labour the midwives instructed the mothers to breathe from the mask during each contraction. During the second stage the mothers were told to take a few breaths from the mask before bearing down.

Apparatus.—Nitrous oxide and oxygen (50%) was given from the Entonox apparatus (accuracy $\pm 2\%$) (B.O.C. Ltd.). Methoxyflurane was administered from a Penlon P.D.V. draw-over vaporizer (Longworth Scientific Instruments Ltd.) with a Ruben one-way valve fitted to the outlet port. The vaporizer control was fixed to deliver 0.35% methoxyflurane, the calibration being checked at intervals by gas chromatography. The accuracy of this apparatus under different conditions of ventilation has been previously investigated (Major *et al.*, 1967).

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