A CLINICAL STUDY OF METHYL-*N*-PROPYL ETHER (NEOTHYL®)

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SINCE THE INITIAL REPORT of the anaesthetic action of methyl-*n*-propyl ether on animals, published by Krantz, Evans, Carr, and Kibler¹ in 1946, this agent has been thoroughly investigated, documented, and tried. Both in the United States and in the United Kingdom the clinical use of this drug has not achieved much popularity in spite of encouraging published reports. Methyl-*n*-propyl ether was first administered to a volunteer in 1945, by the open drop method, and since then there have been many changes in techniques. Renewed acquaintance with the drug suggested that this promising but neglected anaesthetic deserved review.

Methyl-*n*-propyl ether, known as Neothyl® in the United Kingdom and as Metopryl® in the United States, is a simple isomer of diethyl ether:

It is a colourless liquid with a boiling point of 39° C. and a specific gravity of 726 at 16° C. It is coloured green for clinical use and has an ethereal odour. The oil/water coefficient is 10. It is soluble in water, 5 c.c. in 100 c.c. of water. The inflammability range is identical with that of diethyl ether. Oxidation is encouraged by heat, light, and air, and prevented by storage in sealed, dark glass bottles.

Experiments with a variety of animals by White, Shane, and Krantz in 1946² revealed no liver or kidney damage. They also found no damage to the cardiovascular system, an absence of changes in the ECG, and unaffected pulse rate and blood pressure at acceptable levels of anaesthesia. Induction and recovery proved to be rapid. When administered to human patients the findings were similar. Rees and Gray in 1950³ found that circulatory changes were unusual except in deep anaesthesia when profound hypotension might occur suddenly, with or without bradycardia. Elimination from the body is accomplished by the lungs without change and recovery is more rapid and less eventful than with diethyl ether. Elevation of blood sugar levels occurs as with diethyl ether, but return to normal is possibly faster.

This series initially consisted of only healthy multiparous obstetrical patients, whose delivery, spontaneous or by low forceps, was obviously imminent. Experience gained with these patients encouraged some broadening of the selection to include all obstetrical patients not exhibiting clear-cut contraindications to the

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use of this drug—i.e., those whose labours were prolonged, who were severely toxic or vomiting excessively—and any patients undergoing surgery that would require the use of electrical appliances. The ages ranged from 13 months to 72 years. See Tables I to IV.

TABLE I
AGE DISTRIBUTION OF ALL CASES

Age, years	Obstetrical patients	Surgical patients
1-20	3	3
20-30	97	3
30-40	51	13
40+	4	30
Totals	155	49

TABLE II
VARIETY OF OBSTETRICAL PROCEDURES

Type of procedure	Number of patients
Spontaneous delivery	102
Low forceps	33
Rotation and forceps	12
Breech	6
Twins	2
Total	155

TABLE III
DISTRIBUTION OF SURGICAL PROCEDURES

Type of procedure	Number of patients
Operations on extremities	18
Abdominal operations	12
Perineal operations	17
Head and neck operations	2
Total	49

TABLE IV
ANALYSIS OF ABDOMINAL PROCEDURES

Type of procedure	Number of patients
Hysterectomy	8
Cholecystectomy	1
Polypectomy (from descending colon)	1
Appendectomy	1
Presacral neurectomy	1
Total	12

All surgical patients received a conventional pre-operative narcotic with atropine or hyoscine one hour before induction. Obstetrical patients received a wide variety of analgesics and sedatives, except a few patients whose labour was too rapid to permit sedation. There were a few patients who received no atropine or hyoscine prior to induction.

The method of administration varied according to the circumstances and the procedure. At the beginning of the series, the wick ether vaporizer in the standard Heidbrink machine was used for all obstetrical cases. Later both the ether vaporizer and the Rowbotham bottle on the Boyle machine were used with the semi-closed system. The Rowbotham bottle, filled 5 c.c. over the mark, was sufficient for most obstetrical procedures lasting 30–45 minutes, but the depth and duration of anaesthesia were limited. For procedures requiring longer or deeper anaesthesia the ether vaporizer was preferred, with the closed system to minimize escape of vapour. All of the surgical patients received a conventional induction with thiopentone, followed by the gradual introduction of methyl-*n*-propyl ether, after intubation if required by the nature of the operation, or at such times as the anaesthetist felt this was indicated. The amounts used varied widely, from 5 c.c. to 25 c.c. for deliveries, the usual amount being 15–20 c.c. for 30–45 minutes. The smallest amount given to a surgical patient was less than 5 c.c. (to potentiate *d*-tubocurarine) and the greatest was 150 c.c.

OBSTETRICAL PATIENTS

The 155 obstetrical patients included 31 primiparae and 124 multiparae, all of whom had labours normal in character and duration. Forty-five of these vomited or retched, but salivation occurred only twice, even without previous atropine, and coughing was rare and caused no difficulty. Seven of those who vomited did so during the induction and the anaesthetic had to be discontinued. Of these seven, four had received their sedation too late, one had no sedation, and two were adequately sedated.

Blood pressure changes of varying degree were exhibited during delivery, but did not differ from the pattern of changes seen during other deliveries. Of six patients who had shown mild toxæmia during pregnancy, two had a fall of pressure which brought them to normal levels, with no ill-effects.

In the third stage, the incidence of complications was as shown in Table V.

TABLE V
COMPLICATIONS OF THE THIRD STAGE OF LABOUR

Complications	Number of patients
Retained placenta	7
Post-partum haemorrhage, 500–1,000 c.c.	11
Post partum haemorrhage, over 1,000 c.c.	6
Total	24

Only three of those with retained placenta fulfil the criterion that the placenta is undelivered after 30 minutes. Three were removed manually to control bleeding from a flaccid uterus. One placenta was retained as a result of the intravenous administration of ergometrine. Two of the cases with retained placenta are also included in the group with post-partum haemorrhage under 1,000 c.c., and one case is also included in the group with more massive haemorrhage.

TABLE VI
ASSOCIATED FACTORS IN CASES WHERE BLOOD LOSS WAS MORE THAN 1,000 C.C.

Parity	Duration of labour, hr.	Other factors	Weight of infant, lb.	Amount of methyl-n-propyl ether, c.c.
0	2	Retained placenta	6-8	56
i	Rapid	Previous section	6-8	77
0	10	Twins	5½ each	14
i	3½		9½	28
i	6		8½	14
ii	Unknown		8½	35

TABLE VII
ASSOCIATED FACTORS IN CASES WHERE BLOOD LOSS WAS BETWEEN 500 AND 1,000 C.C.

Parity	Duration of labour, hr.	Other factors	Weight of infant	Amount of methyl-n-propyl ether, c.c.
i	12	Previous section	6-8 lb.	77
0	12	Fundal pressure to assist delivery	6-8 lb.	56
i	12	Occipito-posterior	9 lb.	21
ii	7	Maternal weight 195 lb.	7 lb.	23
i	4	None	6-8 lb.	28
i	12	Uterus observed to relax	6¼ lb.	35
i	3	Uterus relaxed after delivery of placenta	Not known	Not known
i	5	None	6 lb.	14
i	12	None	7 lb.	42
i	7	Retained placenta	8 lb. 7½ oz.	35
ii	5	None	9½ lb.	140

TABLE VIII
APGAR ASSESSMENT OF BABIES AT SIXTY SECONDS AFTER DELIVERY

Apgar rating	0	1	2	3	4	5	6	7	8	9	10
Number of babies	4	0	1	3	3	2	8	9	35	40	51
Average 8 46											

TABLE IX
FACTORS OTHER THAN ANAESTHESIA INFLUENCING LOW APGAR ASSESSMENT

Stillbirth with gross congenital abnormalities	3
Premature delivery with APH (stillbirth)	1
Difficult labour	3
Difficult delivery—breech	3
Difficult delivery—forceps	1
Cord tightly around neck	1
No obstetrical reason obvious	1
Total	13

SURGICAL PATIENTS

Among the 49 surgical patients are included those at the extremes of age, with the majority over 40 years. A variety of coincident pathology was shown in this

group (see Table X), no adverse effects appearing in the course of the anaesthesia. Since anaesthesia for all these patients was induced with intravenous barbiturate after conventional premedication, the inductions were quiet.

TABLE X
COINCIDENTAL PATHOLOGY IN SURGICAL PATIENTS

Pathology	Number of patients	
Obesity	10	
Hypertension	2	
Cardiac lesions	4	(1) Old rheumatic fever (2) Old infarct (3) Arteriosclerosis (4) Arteriosclerosis
Respiratory lesions	2	(1) Asthma (2) Healed T.B.

Introduction of methyl-*n*-propyl ether into the system produced an occasional slight, short cough which was relieved by reducing the concentration. The eight patients undergoing hysterectomy were given methyl-*n*-propyl ether with the intention of potentiating the muscle relaxant (*d*-tubocurarine) already in use. All were large, heavy women who were proving difficult to anaesthetize satisfactorily with the usual technique (thiopentone - nitrous oxide - relaxant sequence). In the other intra-abdominal procedures methyl-*n*-propyl ether was used for analgesic as well as potentiation of relaxant.

TABLE XI
BLOOD PRESSURE CHANGES IN SURGICAL PATIENTS

Change in systolic blood pressure	+30	+20	+10	-10	-20	-30
Number of patients	3	4	17	12	16	5

Investigation of the five in Table XI whose systolic blood pressure fell 30 points brought out the following facts:

1. The fall in blood pressure followed the administration of thiopentone, before methyl-*n*-propyl ether was introduced.
2. Large quantities of thiopentone, meperidine, and perphenazine had been given before methyl-*n*-propyl ether was used. A gradual fall occurred during a three-hour procedure.
3. Blood pressure was elevated by apprehension beforehand. The fall represented a quiet return to normal level.
4. The fall of blood pressure was recorded in the recovery room. This patient had received $3\frac{3}{4}$ oz. of methyl-*n*-propyl ether.
5. The fall of 30 mm. Hg occurred after the patient had been in the lithotomy position for a vaginal repair.

The recovery period of the surgical group was relatively uneventful. Two patients were restless and five vomited. Waking time varied considerably in both groups, being influenced by the variety of other drugs used concurrently (see Table XII). Obstetrical patients particularly appeared to experience a quiet and

rapid awakening. Prolonged drowsiness was confined to those who had been heavily sedated.

TABLE XII
DIFFERENCE IN WAKING TIME BETWEEN SURGICAL AND OBSTETRICAL PATIENTS

Minutes	1	2	3	4	5	10	15	20	25	30	30+
Surgical patients	2	1	1	1	5	12	5	1	1	1	18
Obstetrical patients	25	24	14	5	23	24	5	8		1	12

DISCUSSION

Methyl-*n*-propyl ether, when vaporized, is a colourless gas which has all the explosive properties of the isomer diethyl ether, and its usefulness is limited by this factor. However, the pungent ethereal odour gives warning of leaks from a closed system, so there is no possibility of a pool of explosive vapour forming unnoticed. When methyl-*n*-propyl ether has been vaporized in a clear glass vaporizer, an interesting phenomenon can be observed once the methyl-*n*-propyl ether has been excluded from the system. Vaporization continues slowly, and the deepening layer of vapour, itself colourless, carries a ring of green colour on its surface.

Induction with the non-irritating vapour is almost free from coughing and salivation. Even among patients who have not received atropine, secretions rarely prove an embarrassment. The transition from thiopentone to methyl-*n*-propyl ether is usually quiet, but surgical stimulation may provoke movement. In properly prepared patients, induction with the vapour is smooth and rapid, permitting not only spontaneous obstetrical delivery but even outlet forceps delivery only three minutes after induction has been started. The emphasis here is on proper preparation. Patients who have received no sedative, have received sedative too late, or are already excited do not experience a smooth induction. Under those circumstances, induction is prolonged and the patient is likely to resist vigorously. A small sleep-dose of pentathol can alleviate the situation, but has its own disadvantages. A number of obstetrical patients were given methyl-*n*-propyl ether with nitrous oxide during contractions, but the room soon became filled with explosive vapour and this technique was discarded early. Moreover, the occasional hallucinations experienced by these patients far surpassed those occurring with nitrous oxide and oxygen alone. In this respect, trichloroethylene would appear to be superior, since it is less likely to explode, but startling hallucinations can also occur with this agent. Among the unsatisfactory inductions are those seven complicated by vomiting. Only two appeared to be adequately sedated, so improper sedation may have had some bearing on these episodes.

The condition of the infants as indicated by Apgar rating appears quite satisfactory (see Table VIII). Of the 13 whose rating was less than 6, 12 had clear obstetrical reasons for depression. The four stillbirths were unrelated to anaesthesia. Methyl-*n*-propyl ether could be considered to have increased the depression, although it is unproved, except for one whose only apparent reason for depression was anaesthesia. In the series of Caesarean Sections reported by B.

Kaplan⁵ in 1951, no infants were depressed unless shocked by obstetrical causes.

With the introduction of an unfamiliar agent, obstetricians ask whether it will stop the contractions and whether it will cause bleeding. Methyl-*n*-propyl ether does not appear to affect the contractions or diminish the patient's expulsive efforts. The induction is not fast enough to achieve this, unless administration is started before delivery is imminent. Certainly, methyl-*n*-propyl ether did not appear to postpone delivery at any time in this series.

The figures for the complications in the third stage do not appear satisfactory (Table XIII). The criterion would appear to be that the placenta should deliver within 30 minutes after the infant and that total blood loss should be less than 500 c.c. Eastman and Hellman⁶ state that blood loss of more than 500 c.c. in 10 per cent of all deliveries and blood loss of more than 1,000 c.c. in 1.5 per cent of all deliveries may occur, and retained placenta in only 1 per cent. Too many of

TABLE XIII
PERCENTAGES OF ABNORMAL THIRD STAGES

Retained placenta	4 5%
Blood loss 500-1,000 c.c.	7 09%
Blood loss 1,000 c.c. or more	3 87%

the patients of this series had a retained placenta and too many had blood loss in excess of 1,000 c.c. However, there were 46 obstetricians participating in this series, one of whom always explores the uterus manually and does not wait 30 minutes for delivery of the placenta. At the same time, there was no uniformity in management of the third stage, nor was there complete accuracy in measurement of blood loss. However, on the basis of the figures available, the influence of methyl-*n*-propyl ether must be considered. Eastman and Hellman list among their causes of post-partum haemorrhage, infants larger than 9 lb., twins, operative delivery, deep ether anaesthesia, and prolonged labour and exhaustion. These are represented in the group (3.87%) who lost more than 1,000 c.c. of blood, except deep ether anaesthesia, prolonged labour, and exhaustion. Methyl-*n*-propyl ether is more potent than diethyl ether, and all the patients in this group had received more than 1 oz. of methyl-*n*-propyl ether, except one, whose infant was large, almost nine pounds. The usual amount required for a delivery was $\frac{1}{2}$ oz. to $\frac{3}{4}$ oz. It is not clear whether the difficult third stage required more anaesthesia or that too much anaesthesia made a difficult third stage.

Except for the patients mentioned in the previous paragraph, none were deeply anaesthetized, since 15-25 c.c. of methyl-*n*-propyl ether, easily contained in the Rowbotham bottle, is sufficient for a delivery lasting up to about 45 minutes but is insufficient for deep anaesthesia. Two of the obstetrical patients were inadvertently put into a state resembling ether analgesia. They talked cheerfully and apparently sensibly throughout repair of the episiotomy, stated that they were comfortable, and felt no pain. Within one minute of removing the mask, they became fully conscious and enquired about their babies, but did not remember their deliveries. This might have resulted from the gradual reduction in concentration of the vapour as the fluid level in the vaporizer subsided.

Methyl-*n*-propyl ether proved satisfactory in all surgical cases in this series, and would doubtless have been equally satisfactory in a greater number of cases undergoing head and neck surgery, such as tonsillectomies, had the surgeon not found the odour intolerable.

In the recovery room the odour of exhaled methyl-*n*-propyl ether was as easily noticeable as that of diethyl ether, but the recovery period on the whole was satisfactory. Variation in blood pressure at this time is not unusual, and these patients were not unusual in this respect. One fall in blood pressure was probably due to the large amount of methyl-*n*-propyl ether used ($3\frac{3}{4}$ oz.). This was not the largest amount to be administered, but in this case appeared to be responsible for the hypotension, from which the patient recovered spontaneously.

CONCLUSIONS

Methyl-*n*-propyl ether would appear to be a useful agent under the following conditions:

1. When appropriate precautions have been taken to avoid explosion.
2. When patients have received suitable premedication the usual length of time before induction.
3. When caution is exercised during the third stage to minimize the risk of post-partum haemorrhage.

Methyl-*n*-propyl ether is particularly useful in uncomplicated spontaneous or low forceps deliveries and as an adjunct to thiopentone – nitrous oxide – relaxant sequence to smooth the course of anaesthesia in heavy patients whose anaesthetic status is difficult to stabilize.

SUMMARY

Methyl-*n*-propyl ether was used to anaesthetize 155 obstetrical patients and 49 surgical patients. The obstetrical procedures were of all types except Caesarean Section, and the surgical procedures included operations on the extremities and perineum, and eight abdominal operations. In these abdominal operations, methyl-*n*-propyl ether was used as an adjunct to the thiopentone – nitrous oxide – relaxant sequence, whereas it was the principal anaesthetic agent in the obstetrical cases.

Both closed and semi-closed systems were used. All surgical patients had received the usual premedication one hour beforehand and anaesthesia was induced with thiopentone. Premedication for the obstetrical patients was very variable. Some received no atropine but this proved to be no disadvantage since secretions were not troublesome during induction.

In most cases induction, anaesthesia, and recovery were uneventful, but improperly sedated obstetrical patients proved difficult to anaesthetize.

Vomiting was not frequent enough to be a problem. Infants were not born depressed, the average Apgar rating being 8.46.

A slightly increased incidence of difficulty in the third stage is shown in this series and the influence of methyl-*n*-propyl ether cannot be completely exonerated.

RÉSUMÉ

Nous avons employé l'éther méthyl-*n*-propyl comme agent anesthésique au cours de 155 cas d'obstétrique et 49 cas de chirurgie. Les cas d'obstétrique comprenaient différents types de cas à l'exception de la césarienne, et les cas de chirurgie comprenaient des opérations sur les extrémités, le périnée et huit cas d'opérations abdominales. Au cours de ces opérations abdominales, l'éther méthyl-*n*-propyl a été employé comme adjuvant au mélange thiopentone-protoxyde et myorésolutif, alors que, pour les cas d'obstétrique, il était employé comme agent anesthésique principal.

Nous avons employé les deux différents systèmes: fermé et semi-fermé. Tous les cas de chirurgie avaient reçu la prémédication usuelle une heure avant et l'anesthésie était commencée avec le thiopentone. La prémédication pour les cas d'obstétrique variait beaucoup. Certains cas n'ont pas reçu d'atropine, mais cela n'a pas été une lacune puisque les sécrétions n'ont pas causé d'ennuis au cours de l'induction.

Dans la plupart de cas, l'induction, l'anesthésie et le réveil se sont passés sans incidents mais, dans les cas d'obstétrique où la sédation était insuffisante, les malades ont été difficiles à anesthésier.

La fréquence des vomissements n'a pas été assez grande pour poser un problème. Les enfants sont nés sans être déprimés, la moyenne de la formule Apgar a été de 8.46.

Au troisième stage, des difficultés sont apparues un peu plus souvent au cours de cette série et l'on ne peut pas mettre de côté complètement l'influence de l'éther méthyl-*n*-propyl.

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